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Advancements in medical technology coupled with a more thorough comprehension of oncologic diseases has resulted in a burgeoning number of aggressive treatment options available to cancer patients and a gradual loosening of the association between cancer and timely death. With the advent of extended life expectancies, however, the need to investigate the human and overall life impact of cancer diseases and treatments has increased dramatically (Langenhoff et al., 2001). This need to examine considerations of *quality* of life becomes even more essential in the context of high-risk treatments, such as cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS+HIPEC), an extensive procedure offered to select candidates with peritoneal carcinomatosis from a variety of primary origins (Levine et al., 2007). A biopsychosocial model of research and clinical care (e.g. Wilson & Cleary, 1995) underscores the many levels and interrelationships of clinical, demographic, and psychosocial variables impacting survivors of such an invasive medical procedure, yet a paucity of methodologically sound psychosocial studies with these long-term CS+HIPEC survivors exists.

The purpose of this investigation was to enhance our understanding of the multidimensional quality of life (QOL) and sleep quality of survivors who have lived 12 or more months post-CS+HIPEC. Additionally, the contributions of surgical and biological variables to long-term QOL were examined, as were changes in QOL scores

over time in a subset of the sample. This descriptive data acquired enriches our knowledge of CS+HIPEC survivors' quality of survivorship, informs prospective candidates' treatment decision making processes, and enhances the standard of care by serving as a foundation for future psychosocial interventions.

QUALITY OF LIFE AND SLEEP QUALITY OF LONG-TERM SURVIVORS OF
CYTOREDUCTIVE SURGERY PLUS HYPERTHERMIC INTRAPERITONEAL
CHEMOTHERAPY

By

Katharine E. Duckworth

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Approved by

Committee Chair

APPROVAL PAGE

This dissertation has been approved by the following committee of the Faculty of
The Graduate School at The University of North Carolina at Greensboro.

Committee Chair _____
Dr. Craig S. Cashwell

Committee Members _____
Dr. Kelly Wester

Dr. Robert Henson

Nancy Callanan

Date of Acceptance by Committee

Date of Final Oral Examination

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TABLE OF CONTENTS

	Page
LIST OF TABLES	viii
LIST OF FIGURES	xi
CHAPTER	
I. INTRODUCTION	1
Quality of Life.....	3
A Biopsychosocial Model.....	5
CS+HIPEC as a Treatment of Peritoneal Carcinomatosis	6
Sleep Quality.....	9
Purpose of the Study	10
Statement of the Problem.....	11
Research Questions	12
Need for the Study	13
Definition of Terms.....	19
Brief Overview.....	23
II. LITERATURE REVIEW	24
Introduction.....	24
Prevalence and Incidence Data	25
Prevalence and Incidence of Peritoneal Carcinomatosis	28
Cytoreductive Surgery + Hyperthermic Intraperitoneal Chemotherapy (CS+HIPEC)	30
Peritoneal Metastases.....	30
Rationale for CS+HIPEC.....	33
Cytoreductive Surgery	36
Intraperitoneal Chemotherapy	38
CS+HIPEC at Wake Forest University Baptist Medical Center	41
Factors Associated with Success	43
Risks and Toxicity	44
Survivorship in Oncology	47
Survivorship Research	49
Quality of Life (QOL) as an Outcome Measure	51
Challenges in Researching QOL.....	59

Entry of QOL into Clinical Trials	60
QOL of Patients Receiving CS+HIPEC	62
Acute QOL	64
Long-term QOL	70
The QOL of subgroups	72
Case study	73
Sleep Quality	76
The Body During Sleep	80
Effects of sleep on the body	86
Effects of the body on sleep	88
Sleep deprivation	94
Sleep Quality of Cancer Survivors	97
Sleep quality of CS+HIPEC recipients	103
The Wilson and Cleary Model	105
Limitations of Research on QOL in Survivors of CS+HIPEC	117
Conclusion	123
 III. METHODOLOGY	 125
Research Questions and Hypotheses	125
Participants	127
Instrumentation	128
Medical Outcomes Study 36-item Short Form Health Survey (SF-36)	129
Physical Functioning (PF) scale	132
Role Emotional (RE) and Role Physical (RP) scales	132
Bodily Pain (BP) scale	133
General Health Perception (GH) scale	133
Vitality (VT) scale	133
Social Functioning (SF) scale	134
Mental Health (MH) scale	134
Reported Health Transition (RHT)	134
Pittsburgh Sleep Quality Index (PSQI)	139
Patient Information Questionnaire	148
Demographic Questionnaire	149
Procedures	149
Data Analysis	152
Pilot Study	154
Feedback	155
Summary	158
 IV. RESULTS	 159
Sample Characteristics	159

Instrument Psychometrics	163
Hypothesis Testing.....	163
Research Question 1	164
Research Question 2	168
Research Question 3	172
Research Question 4	175
Research Question 5	179
Hypothesis one.....	179
Hypothesis two.....	181
V. CONCLUSIONS.....	184
Overview	184
Discussion	184
Limitations of the Study.....	196
Implications for Counseling.....	199
Suggestions for Future Research	202
Conclusions.....	204
REFERENCES	207
APPENDIX A: INSTRUCTIONS AND CONSENT FORMS	222
APPENDIX B: PERMISSIONS AND INSTRUMENTS	231
APPENDIX C: PILOT STUDY METHODS AND RESULTS	256
APPENDIX D: ADDITIONAL ANALYSES	274

LIST OF TABLES

	Page
Table 1: Research Questions, Hypotheses, Variables, and Analyses	153
Table 2: Descriptive statistics: Current Age, Age at CS+HIPEC, Months since Surgery	161
Table 3: Descriptive Statistics: Resection Status.....	161
Table 4: Descriptive Statistics: Gender.....	161
Table 5: Descriptive Statistics: Ethnicity.....	161
Table 6: Descriptive Statistics: Race	162
Table 7: Descriptive Statistics: Primary Cancer Site	162
Table 8: Descriptive Statistics: Marital Status.....	162
Table 9: Internal Consistency of Measures.....	163
Table 10: Quality of Life: Norm-based Scores and Confidence Intervals for Mean Scores	165
Table 11: Quality of Life: Z-statistics and p-values	166
Table 12: Paired t-test: Change at follow-up, Physical Functioning	168
Table 13: Paired t-test: Change at follow-up, Role Physical	168
Table 14: Paired t-test: Change at follow-up, Bodily Pain	169
Table 15: Paired t-test: Change at follow-up, General Health.....	169
Table 16: Paired t-test: Change at follow-up, Vitality	169
Table 17: Paired t-test: Change at follow-up, Social Functioning.....	169
Table 18: Paired t-test: Change at follow-up, Role Emotional	170
Table 19: Paired t-test: Change at follow-up, Mental Health	170

Table 20: Paired t-test: Change at follow-up, Physical Component	170
Table 21: Paired t-test: Change at follow-up, Mental Component	170
Table 22: Pittsburgh Sleep Quality Index Means	172
Table 23: Pittsburgh Sleep Quality Index Frequencies.....	173
Table 24: Pittsburgh Sleep Quality Index Cutoff Percentages and Confidence Intervals.....	174
Table 25: T-test: Comparison of Pittsburgh Sleep Quality Index Mean Scores Current Sample with Other Populations	175
Table 26: Pearson Correlation Coefficients: Sleep Quality and Quality of Life	176
Table 27: Analysis of Variance: Physical Component Scores, No Interaction	180
Table 28: Analysis of Variance: Mental Component Scores, No Interaction.....	181
Table 29: Physical Component Scores for Appendiceal and “Other” Groups	182
Table 30: Mental Component Scores for Appendiceal and “Other” Groups.....	183
Table A: Sociodemographic Description of the Pilot Study Sample.....	266
Table B: Means and Medians of SF-36 Subscales.....	267
Table C: Norm-based Physical Component Scores of the SF-36	268
Table D: Norm-based Mental Component Scores of the SF-36.....	269
Table E: Pearson Correlation Coefficients, SF-36 Subscales	270
Table F: Scale Reliability and Homogeneity Estimates	270
Table G: Change at follow-up: PF, RP, and BP	270
Table H: Pittsburgh Sleep Quality Index Global and Subscale Scores	271
Table I: Pittsburgh Sleep Quality Index Global Score Mean Comparisons	271
Table J: Pittsburgh Sleep Quality Index Clinical Cut-off >8.....	272

Table K: Correlations: Quality of Life Subscale Scores and Global Sleep Quality Scores	272
Table L: Means by Resection Status.....	273
Table M: Estimation of Scores: Physical Component Scores, No Interaction	275
Table N: Estimation of Scores: Mental Component Scores, No Interaction	275

LIST OF FIGURES

	Page
Figure 1: Wilson and Cleary's conceptual model (1995) of patient outcomes.....	108
Figure 2: Norm-based QOL Subscale and Component Scores.....	166
Figure 3: Changes in QOL Scores over Time.....	171
Figure A: Norm-based Subscale Scores of Pilot Sample.....	267
Figure B: Norm-based Physical Component Scores.....	268
Figure C: Norm-based Mental Component Scores	269

CHAPTER I

INTRODUCTION

“[W]hen one is faced with cancer, the valiant action is to fight. It is our duty to take up arms, to go into battle, to join others in the fight. To do less is somehow less heroic, less honorable. We are at war with cancer...”

(Edes, 2008, p. 2483)

Under the guise of an often underestimated influence, cultural metaphors and diction stealthily infiltrate our individual and collective perceptions, layering us with implicit pressures that seep in and guide our actions. Albeit not always negative, these existing messages warrant additional attention when their presence sways and potentially prioritizes one life-altering decision (i.e., seeking treatment) over another that is equally valid (i.e., not seeking treatment). In cancer treatment, those who elect treatment are rightfully revered; yet, acknowledging the heroism of those who choose death, death preceded by months or years of quality, is equally warranted. Edes (2008) eloquently elucidated the reasoning underpinning some patients’ decisions not to seek treatment in the following: “When at war, you must focus on the enemy, not on the beauty of the world around you. When in battle, you must be constantly vigilant for signs of danger, not distracted by opportunities for joy. When preparing to fight you must be disciplined and attuned to the mission, not relaxing with family” (p. 2483). For those who are

diagnosed, no treatment-related decision is “right” and none is “wrong”. Electing not to undergo extensive treatment, however, is far from losing a fight. For some, it is personifying the belief that there are more important things to do with precious time. Every individual deserves to make the decisions that optimally suit her or his goals, and the availability of accurate quality of life data alongside the existing quantity of life data is one way to equip individuals with holistic knowledge for making informed decisions.

Researchers investigating the impact and efficacy of oncology treatments examine a vast array of patient variables that become increasingly complex and integrated as focus broadens from the single cell and organ systems, to the holistic individual, to ultimately the individual functioning in a micro/macrocism (Wilson & Cleary, 1995). Researchers may focus on biological or physiological variables (e.g., neutrophil count, pulmonary function test results), treatment-related morbidity or psychological symptoms (e.g., fatigue, anhedonia), functional impairments (e.g., difficulties bathing or climbing stairs), subjective ratings of health perception, overall quality of life ratings, or mortality rates and survivorship experiences. Treatment “success,” then, may be quantified using any of the aforementioned. Researchers from different disciplines often diverge in their opinions of which outcome variables should be prioritized and, to further confound the situation, medical clinicians and patients also may prioritize alternate outcome variables (e.g., survival rate versus psychosocial impact). These differing priorities may never emerge in doctor-patient dialogue (Halyard & Ferrans, 2008), despite the fact that treatment selections may vary based on the outcome measure perceived to be of most importance.

In the not-so-distant past, oncology treatments were grossly measured only in terms of death, cure, and toxicity rates (Cella & Tulsky, 1993; Langenhoff, Krabe, Wobbes, & Ruers, 2001). With advancements in technology, coupled with a more thorough comprehension of oncologic diseases, a burgeoning number of aggressive treatment options are now available to patients. As a consequence, many types of cancer are no longer automatically associated with timely death and minimal life expectancies (Cella et al. 1993), and words/phrases such as *survivorship*, *cure*, and *mounting chronicity* have become widely used in the oncology vernacular. In tandem with this steady shift has been a mushrooming interest on the part of researchers and society alike in learning about the impact of diseases and treatments on patients' and their loved ones' lives (Langenhoff et al., 2001). As more cancer patients face cure and extended life expectancies, *quality* of life demands equal emphasis and credence in treatment evaluation compared to *quantity* of life.

Quality of Life

Quality of life (QOL) is a concept with roots dating back to antiquity, yet a definition of the term as well as valid and reliable tools for its measurement are comparatively recent developments (Cella et al., 1993). Cella and Cherin (1988) defined QOL as "patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal" (p. 70). Most researchers agree that QOL as a construct is subjective, in flux, multidimensional and, ideally, based on the patient's perspective (Cella & Tulsky, 1990). Likewise, it is a dual-sided construct, encapsulating not only downward declines in functioning, but attending also to positive,

wellness aspects of one's current functioning (Cella & Cherin, 1988). The primary dimensions of QOL supported by factor analysis and proposed by Cella et al. (1993) include physical, functional, social, and emotional dimensions. Instruments to measure QOL, then, not only must assess these four domains but must also be sensitive to changes over time (Cella et al., 1993).

When researching patients' QOL in a medical context, it is important to measure objectively the extent of the medical problems, obtain a patient-rated appraisal of the extent of the dysfunction, and assess how the patient's subjective appraisal compares with her or his expectations (Cella et al., 1990). Objective measurements of medical complications allow for quantification of the extent of problems and the acquisition of data detailing distinct advantages and disadvantages of the respective treatment. Objective measurements and even symptom reports alone remain insufficient, however, as the unique effects of these symptoms on life functioning and quality is what is desired by those targeting the psychosocial impact of treatment (Ferrans, 2007). Therefore, the patient's subjective ratings are needed to shed insight into the distress associated with the condition and the degree to which it is tolerable to that respective individual (Cella et al., 1990). Consistently noted in these patient-rated outcomes is a high rate of variability, as patient characteristics and a plethora of additional variables unrelated to patients' biological or physiological well-being impact subjective experiences (Cella et al., 1990). If one acknowledges this myriad of individual appraisals of synonymous objective events (e.g., treatment results or disease progression), however, he or she must, in turn, also

acknowledge the importance of measuring these subjective experiences alongside the “objective” medical reality (Cella et al., 1993).

Numerous professional oncology organizations similarly have recognized the importance of measuring both the objective and subjective realities of patients and have incorporated these ideals into recent guidelines and standards. For example, in their 1995 guidelines for cancer treatment and assessment, The American Society of Clinical Oncology (ASCO) concluded that measuring survival in the absence of other outcome variables is insufficient; “the quality of survival and cost of maintaining or improving it must also be assessed” (American Society of Clinical Oncology, 1996, p. 673). Likewise, in their requirements for approval of new anticancer drugs adopted in 1985, the FDA listed survival and QOL as the two key efficacy parameters (Johnson & Temple, 1985) on which a proposed drug must have a favorable effect in order to be approved. The attention to QOL issues by these aforementioned influential organizations illustrates the collective belief in the importance of attending to issues of quantity (i.e., survival) and quality (i.e., multidimensional life impact) in cancer treatment.

A Biopsychosocial Model

Also conceptualizing measures of health as interrelated and existing on a continuum of increasing complexity, Wilson and Cleary (1995) integrated two paradigms, one held by biomedical researchers with one held by social scientists, in their five-level conceptual model of patient outcomes (i.e. biological/physiological, symptom status, functional status, health perceptions, and quality of life). Among other insights, this model highlights the plethora of layered, relational variables (from the single cellular

level outward to more abstract measures of well-being) that impact a survivor's current existence. The equally-important and bidirectional influences of these variables on survivor functioning underscore the need for research and clinical attention to both "hard" and "soft" patient outcome variables in any medical context.

As new and aggressive treatments enter the oncology scene, this equal attention to biological and psychosocial dimensions of functioning becomes especially important for researchers. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS+ HIPEC) is such an example of an aggressive procedure gaining acceptance for patients with intra-abdominal malignancies that have spread throughout the peritoneal cavity (Stewart, Shen, & Levine, 2008).

CS+HIPEC as a Treatment of Peritoneal Carcinomatosis

The peritoneal cavity is the space within the abdomen, bound by thin membranes, that contains the intestines, the stomach, and the liver (National Cancer Institute, n.d.). Peritoneal carcinomatosis occurs following the intracavitary dissemination of tumors from various surrounding areas, including ovarian and gastrointestinal carcinomas and sometimes sarcomas and mesothelioma (Levine et al., 2007). The movement of malignancies into the peritoneal cavity is considered a terminal diagnosis, as this carcinomatosis progressively spreads, ultimately leading to bowel obstruction and subsequent death in approximately six months if untreated (Stewart et al., 2008). Typical systemic therapy (i.e., chemotherapies that travel through the bloodstream and impact cells all over the body; National Cancer Institute, n.d.) is strictly palliative in nature for individuals with peritoneal surface disease, as systemic therapies ineffectively move

through the peritoneal-plasma partition (Stewart et al., 2008). That is, survival is not significantly increased by administration of systemic therapies. Cytoreductive (debulking) surgery alone allows removal of macroscopic disease, thereby preventing short-term bowel obstruction (Sugarbaker, 1989), but microscopic disease inevitably remains in the peritoneal cavity and returns in a matter of time (Stewart et al., 2008). Individuals with peritoneal disease, however, often have no extra-abdominal disease, meaning the disease is concentrated in one regional area. This localization of metastases within the peritoneum in combination with the absence of ancillary metastases makes an aggressive localized approach a suitable option (Stewart et al., 2008).

CS+HIPEC is an aggressive, multimodal technique that offers patients with peritoneal carcinomatosis the possibility of extended life. Surgeons performing this extensive procedure combine cytoreductive surgery (to remove the macroscopic disease) with chemoperfusion (i.e., bathing organs, tissues, or a specific part of the body with high doses of chemotherapeutic agents; National Cancer Institute, n.d.) directly into the peritoneal cavity to attack the microscopic and residual disease (Levine et al., 2007). Chemoperfusion administered immediately following CS is advantageous for numerous reasons (Levine et al., 2007). First, administering intracavitary chemoperfusion allows the tumors to be exposed to drug levels much higher than those achievable with standard systemic therapy. Second, the peritoneal surfaces are all exposed following the CS, so drug distribution is more efficient. Finally, by not administering numerous cycles of systemic therapy, the patient is not exposed to repeated bouts of chemotherapy and related morbidities (Levine et al., 2007).

Adherence to stringent patient selection criteria is essential for attainment of positive post-CS+HIPEC outcomes and, even in the best of circumstances, morbidity and mortality rates remain high (Stewart et al., 2008). Specifically, in a review of 501 procedures on 460 patients, Levine et al. (2007) reported a 4.8% 30-day mortality rate, 43% morbidity rate, 22.2-month median survival, and five-year survival rate of 27.8%. The primary tumor site (Levine et al., 2007), resection status (i.e., the achieved level of visible tumor removal and cytology findings post-operation, as classified by the following: RO- total removal of all visible tumor and negative cytologic findings or microscopic margins; R1- total removal of all visible tumor and positive postperfusion cytologic findings or microscopic margins; R2a- slight amounts of remaining visible tumor, nodules measuring less than or equal to 0.5 cm; R2b- large amounts of visible tumor remaining and nodules greater than 0.5 cm but less than or equal to 2 cm; R2c- gross disease remaining with nodules greater than 2 cm; Levine et al., 2007) and pathological characteristics of the respective individual's disease (Yan, Black, Savady, & Sugarbaker, 2007), among other variables, introduced additional variability in postoperative outcomes and prognoses. Without this procedure, however, all individuals with peritoneal carcinomatosis have grim survival expectancies.

Despite the treatment's existence for over 20 years, limited behavioral science studies have been conducted with individuals who have opted for this procedure (McQuellon & Duckworth, 2009). Understanding the QOL impact of this aggressive procedure on survivors will inform treatment evaluation, health team behavior and care,

future patient decision-making and expectation adjustment, and post-operative psychosocial interventions designed for these patients and their families.

Sleep Quality

Also important and largely understudied within this population is sleep quality, a specific component of QOL that largely impacts patients' well being. Unlike other psychosocial and biopsychosocial variables associated with cancer treatment, sleep quality remains understudied in cancer patients, potentially because it is conceptualized as a normal or transitory reaction to diagnosis or treatment or as a secondary reaction to an alternate psychological or medical problem (Savard & Morin, 2001). Sleep concerns in the context of cancer care may trace their roots to any number of factors, including predisposing factors (e.g., a personal history or psychological disorder), factors that only recently triggered their onset (e.g., adjusting to diagnosis, pain), and factors that maintain disordered sleep (e.g., hindering sleep behavior) (Savard & Morin, 2001). In addition to its association with QOL, sleep quality has been associated with shorter life expectancy, immunosuppression, mood disorders and fatigue (Savard & Morin, 2001). In one of the few studies examining the QOL of long-term (i.e., three or more years post-treatment) survivors of CS+HIPEC, McQuellon et al. (2003) noted that poor sleep was one of the top three psychosocial concerns of participants within the timeframe of one month prior to the study. Despite this finding, a paucity of data exists relative to the sleep quality of persons who have received CS+HIPEC. Collecting QOL and sleep quality data on individuals who have received this procedure will be advantageous for surgeons, patients, and the mental health clinicians working with them.

Purpose of the Study

The purpose of this study was to gather more descriptive demographic, QOL, and sleep quality information on CS+HIPEC survivors one or more years post-procedure, as a paucity of information on these long-term survivors currently exists. More specifically, the intent was to attain a multidimensional understanding (by means of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36); Ware & Sherbourne, 1992) of the following dimensions of QOL:

- limitations in physical activities because of health problems;
- general mental health (including psychological distress and well-being);
- limitations in social activities because of physical or emotional problems;
- limitations in usual role activities because of physical health and emotional problems;
- bodily pain;
- vitality (including energy and fatigue);
- general health perceptions

A comprehensive understanding of sleep quality and sleep disturbances in CS+HIPEC survivors also was obtained via administration of the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Further, since pre-surgery QOL data was collected by alternate WFUBMC-affiliated researchers from a subset of individuals who received CS+HIPEC, statistical analyses allowed an examination of changes in QOL across the time period since surgery for this subset of participants. The 12 or more month QOL scores also were compared to population norms.

Statement of the Problem

Despite the introduction of CS+HIPEC into the surgical oncology scene over 20 years ago and its outlook as a promising multimodal therapy for individuals with peritoneal carcinomatosis (Sticca, 2003), few QOL studies of this population have been performed (McQuellon & Duckworth, 2009). Specifically, following a review of the literature, only nine QOL studies of this population were located. Of these nine studies, many were methodologically flawed or had an insufficient sample size from which to draw any reliable statistical or clinical conclusions (McQuellon & Duckworth, 2009). Further, patients 12 or more months post-treatment remain inadequately represented within these studies.

Subsumed under and largely impacting QOL, Kvale and Shuster (2006) noted the tendency for cancer patients to underreport sleep-related concerns, despite high estimates of cancer-related insomnia. Sleep disturbances negatively impact patients' QOL by means of heightening patients' senses to suffering in any or all realms of their lives, reducing coping abilities, increasing their sense of pain and general malaise, and altering disease severity perceptions (Kvale & Shuster, 2006), yet many patients are not systematically asked about the quality of their sleep (Savard & Morin, 2001).

Concurrently, Berger, Sankaranarayanan and Watanabe-Galloway (2007) noted the overall dearth of scrupulousness in sleep disturbances measurement within the cancer field in general and the disturbing trend for those clinicians who do measure sleep quality in adults with cancer to do so via a non-comprehensive, one-item statement. Measuring solely one parameter of sleep quality is insufficient (Berger et al., 2007), as this does not

capture the detailed nature of the problem or how it changes over time. Utilization of a brief, yet psychometrically sound, instrument, however, elucidates the prevalence and nature of sleep disturbances within the population so these concerns do not remain underreported (Kvale & Shuster).

A mental health professional working in psychosocial oncology and hospice strives to better understand the QOL of understudied populations and ultimately apply that understanding in means useful to the patients, from diagnosis through treatment and into survivorship. As surgical oncologists continue to hone both their understanding and multimodal treatment of peritoneal carcinomatosis, behavioral scientists and clinicians must keep pace. A clearer understanding of the QOL and sleep quality of patients undergoing CS+HIPEC is needed at all stages of their cancer journey.

Research Questions

Accordingly, this study is designed to address the following research questions:

1. What are the QOL subscale scores (i.e. Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health, Role Emotional) and component scores (Physical Component Score and Mental Component Score) of participants, as measured by the Medical Outcomes Study 36- Item Short-Form Health Survey (SF-36) instrument, and how do they compare to those of general population norms?

2. Regarding those participants for whom pre-surgical data is available, what differences exist between pre-surgical QOL subscale scores and 12 or more-month QOL scores for participants who received CS+HIPEC and have survived?
3. What is the sleep quality of participants, as defined by one's global and component scores on the Pittsburgh Sleep Quality Index (PSQI)?
4. What relationship exists between sleep quality, age at CS+HIPEC, months since surgery, and QOL subscale scores?
5. What are the respective contributions of resection status (RO/R1, R2a, R2b, and R2c) and primary tumor site in predicting QOL subscale scores at 12 or more months?

Need for the Study

Individuals with peritoneal carcinomatosis can expect dismal outcomes without treatment, typically progressing to death in less than one year (Levine et al., 2008). When faced with the option of certain, impending death or a chance of longer-term survival, many patients will opt for a procedure without hesitancy, regardless of the potential accompanying psychosocial correlates. In such a matter of life or death, where one treatment serves as the only option for extended life, many people may question the utility of studying QOL. For numerous reasons, however, psychosocial data must hold a prominent role in treatment recommendations and decisions.

QOL studies are an essential component of treatment evaluations for a multitude of reasons, one being they provide information not often depicted by measures that target more singular and restricted life aspects, such as physical symptoms (Ferrans, 2007). With QOL measures, one is able to capture more broadly the “ripple effect of the change in symptoms produced by the intervention” (p. 22). For example, instead of assessing pain levels in isolation by means of a singular symptom assessment, QOL instruments acquire information on not only pain levels, but also how this experienced pain diffuses into a survivor’s work life, completion of daily chores, and socialization practices. In other words, the larger life impact of physical and mental symptoms experienced as a consequence of the procedure is obtained via these instruments.

This QOL information can serve as one of many important endpoints for consideration in the evaluation of an aggressive treatment as well as who is considered a suitable and optimal candidate in the first place (Cella et al., 1993). Gathering QOL data from different treatment populations enhances knowledge of the typical trajectory for QOL fluctuations after varying treatments. The availability of this post-treatment QOL information permits patients to be informed consumers and decision-makers as they consider various options of care and also helps them adjust their post-treatment recovery expectations. These data may be especially weighted in the decision making of individuals who are poor surgical candidates to begin with or who enter treatment with a substandard prognosis. These individuals likely have less remaining time to live regardless of treatment, and quality of life should be the ultimate focus in palliative medicine (Kvale & Shuster, 2006).

QOL data also inform researchers, physicians and mental health professionals of the psychosocial needs of post-treatment patients (Cella et al., 1993). Too often, patients travel great distances to receive the CS+HIPEC procedure and then receive little, if any, follow-up when they return home, leaving the biopsychosocial team unaware of how they are faring. Alternately, some individuals may present for follow-up medical visits with needs that are not explicitly addressed in the typical medical encounter. By collecting QOL data and monitoring psychosocial variables, team members acquire detailed information about the multidimensional functioning of the patient. This awareness, in turn, fosters cognizance of and energy towards patients' psychosocial needs on the part of all medical and mental health parties, potentially leading to improved clinician-patient relations (Sugarbaker et al., 1982) and the development of empirically-based interventions.

Sleep quality is one factor impacting QOL that also remains understudied within this population. Serving as an essential refuge for all individuals, sleep additionally offers those who are coping with cancer some reprieve from the pain and psychological burden that they all-too-often confront during their waking hours (Kvale & Shuster, 2006). Kvale and Shuster (2006) described the numerous mechanisms through which an adult cancer patient's behavioral and physiologic rhythms may be disrupted, ultimately impacting sleep quality. Behavioral disruption of sleep may result as a consequence of changes in a patient's normal daily living routine (e.g., less daily activity and more day time spent in bed). Poorly managed pain and physical symptoms may affect sleep onset and maintenance. Additionally, psychosocial stressors (e.g., distress, anxiety and

depression), respiratory compromise (e.g., weakened lung capacity or tumors hindering respiration), and immune system alterations resulting from treatments or advancing disease also may impact the sleep cycle (Kvale & Shuster, 2006). Any or all of the aforementioned factors may contribute to diminished sleep quality, ultimately decreasing overall QOL of CS+HIPEC patients.

A thorough understanding of the sleep quality of these survivors has yet to be captured. Considering the impact of sleep quality on everyday functioning, the increased prevalence of insomnia in persons with cancer and even higher incidences in those with advanced disease (Kvale & Shuster, 2006), and the potential impact of relatively simple psychosocial interventions on patients' sleep quality, sleep quality within the cancer arena deserves more investigation than it often receives via ancillary study questions (Berger et al., 2007). Informed by empirical data relating to post-treatment QOL and sleep quality, mental health professionals will be able to develop psychosocial and symptom management interventions for patrons of this procedure, thereby giving equal weight to the quality and quantity of life concerns.

Unfortunately, an insufficient number of adequately sized, methodologically sound QOL studies with individuals post-CS+HIPEC have been conducted despite the treatment's growing popularity and promise since its inception over 20 years ago (McQuellon & Duckworth, 2009). Numerous reasons exist as to why insufficient QOL studies with this population have been conducted and published. First, only a handful of surgical teams routinely perform this procedure on large numbers of patients each year (Stewart et al., 2008). Researchers first must gain access to these patients and then

realize that many likely have traveled long distances from their homes to seek treatment from these specialized surgeons. Following hospital discharge, these patients then may scatter geographically and be more difficult to contact. In addition to geographical dispersion, only a subset of these patients becomes long-term survivors; the majority will go on to die from their disease (Stewart et al., 2008). A researcher studying longer-term survivors of CS+HIPEC (i.e., one year or more post-surgery) must then realize that a significant number of these patients have already died within this timeframe. Something categorically different about those who survive 12 or more months following surgery therefore likely exists, and those who were never discharged from the hospital or who experienced significant post-treatment morbidity and then death will not be represented in the data. A paucity of data still continues to exist on these longer-term survivors as well.

Next, because of the invasiveness of the procedure, hospital stays often are lengthy, and patients typically experience significant morbidity, even mortality (Stewart et al., 2008). This high degree of post-treatment morbidity impairs patients' functioning and ability to complete study instruments. Completing study instruments may be physically burdensome due to a lack of strength or psychologically burdensome if the respective individual has experienced significant obstacles. The end result of missing or incomplete data, however, is the same. Unfamiliarity with study instruments also may make the instruments appear convoluted or daunting to the patients (Cella & Tulsky, 1993). Explaining instruments and analyzing them for missing data in a timely fashion requires a great deal of time and energy on the part of the researcher. These variables

often combine to make patient recruitment and retention difficult, ultimately leading to small sample sizes. The small cohorts found in many of the aforementioned studies of QOL in patients following CS+HIPEC unfortunately render the finding of statistical and clinical conclusions difficult and make sound generalizations from the data impossible.

A combination of numerous obstacles (including geographical dispersion, significant patient morbidity and mortality, patient burden considerations and incomplete or missing data) complicate the data collection process with patrons of this procedure, yet these obstacles must be strategically overcome. Simply because the invasive treatment has concluded for these individuals, their cancer experiences have not. Patients who follow behind them in the future deserve to have this information at their disposal, while health professionals currently working with those who already have made the journey need to be sufficiently knowledgeable to offer these patients quality medical and mental health care.

In summary, CS+HIPEC is a promising treatment for individuals with peritoneal carcinomatosis, offering the possibility of extended life in the face of an aggressive disease. As the procedure gains acceptance and recognition, more individuals likely will become candidates. Concurrently, behavioral science researchers must do their part to study the QOL and other neglected psychosocial variables, including sleep quality, of these individuals post-treatment to inform patient decision making and informed consent, standardized patient selection criteria and ultimately psychosocial interventions post-treatment.

Definition of Terms

Cytoreductive surgery (CS): An extensive operative procedure performed by surgical oncologists. The ultimate goal is to remove (to the extent that it is both safe for the patient and technically feasible) all gross tumor and involved organs, peritoneum, or tissue (Levine et al., 2007, p. 944).

Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy (CS+HIPEC): The performance of extensive cytoreductive surgery (with the goal of resecting all gross disease) followed by heated chemoperfusion to address remaining microscopic residual tumors (Levine et al., 2007, p. 944).

Hyperthermic intraperitoneal chemotherapy: “After CS [is] completed, peritoneal perfusion inflow and outflow catheters [are] placed percutaneously into the abdominal cavity. Temperature probes [are] placed on the inflow and outflow catheters just outside the exit sites from the abdomen. The abdominal skin incision [is] closed temporarily with a running cutaneous suture to prevent leakage of peritoneal perfusate. A perfusion circuit [is] established... Flow rates of approximately 600/1,000 mL/min [are] maintained using a roller pump managed by the perfusionist. The circuit continue[s] through a single roller pump, through a heat exchanger, and then to the patient. Constant temperature monitoring [is] performed at all temperature probes. Once a stable perfusion circuit [is] established and outflow temperature exceed[s] 38.5 [degrees] C, the chemotherapy [is] introduced into the perfusion circuit. A maximum inflow temperature of 42.5 [degrees]

C [is] tolerated during perfusion, with a target outflow temperature at the pelvis of 40 [degrees] C. The abdomen [is] gently massaged throughout perfusion to improve drug distribution to all peritoneal surfaces. Total planned perfusion time after the initial addition of [the chemotherapeutic agent] is 120 minutes” (Levine et al., 2007, p. 945).

Morbidity: The adverse effects caused by a treatment (National Cancer Institute, n.d.).

Mortality: Death or death rate

Nychthemeron: a 24-hour period

Ostomy: “The surgically formed artificial opening that serves as the exit site for connections that the surgeon has made from the bowel or intestine to the outside of the body” (Thomas, 1997, p. 1370-1371)

Palliative medicine: A branch of medicine that focuses on relieving or alleviating pain and symptoms without curing underlying problems (Thomas, 1997)

Performance status: The Eastern Cooperative Oncology Group standardized criteria used to grade the toxicity, response, or general functional status of oncology patients. The ECOG *performance* scores include zero (fully active, able to perform all

pre-disease activities within impairments), one (some restrictions in physically demanding activities but able to ambulate and perform less strenuous work), two (ambulatory and can take care of self but unable to work; moving around greater than 50% of waking time), three (only limited self grooming is possible; in bed or in a chair greater than 50% of waking time), four (confined to bed or chair; fully disabled; cannot perform self care), five (dead) (Oken et al., 1982).

Perfusion: the bathing of an organ or tissue with a fluid; In regional perfusion, a specific area of the body containing localized cancer receives high doses of chemotherapeutics through a blood vessel (National Cancer Institute, n.d.).

Peritoneal: Of or relating to the parietal peritoneum (the tissue that lines both the abdominal wall and pelvic cavity) and the visceral peritoneum (the tissue that covers most of the organs in the abdomen (National Cancer Institute, n.d.).

Peritoneal carcinomatosis: The spread of intra-abdominal malignancies throughout the peritoneal cavity, resulting in an unvaryingly terminal condition with a median life expectancy of six months (Stewart et al., 2008).

Peritoneal cavity: The space within the abdomen, bound by thin membranes, that contains the intestines, the stomach, and the liver. (National Cancer Institute, n.d.).

Psycho-oncology: A sub-field of oncology and mental health from which specialists examine the psychological, social, and behavioral dimensions of cancer from two vantage points: 1) the psychosocial- the psychological responses of both patients and their family members at all stages of disease, from diagnosis to survivorship; 2) the psychobiological- psychological, social, and behavioral issues that influence morbidity and mortality (Holland, 1998, p. 3).

Quality of life (QOL): QOL refers to “patients’ appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal” (Cella & Cherin, 1988, p. 70)

Resection status: determined post-CS by means of the following classification scheme: “R0, complete removal of all visible tumor and negative cytologic findings or microscopic margins; R1, complete removal of all visible tumor and positive postperfusion cytologic findings or microscopic margins; R2a, minimal residual tumor, nodule(s) measuring < [or equal to] 0.5 cm; R2b, gross residual tumor, nodule > 0.5 cm but < [or equal to] 2 cm; and R2c, extensive disease remaining, > 2cm” (Levine et al., 2007, p. 944)

Sleep quality: “Quantitative aspects of sleep, such as sleep duration, sleep latency, or number of arousals, as well as more purely subjective aspects, such as ‘depth’ or

‘restfulness’ of sleep... [T]he exact elements that compose sleep quality, and their relative importance, may vary between individuals” (Buysse et al., 1989, p. 194).

Systemic therapy: chemotherapies that travel through the bloodstream and impact cells all over the body (National Cancer Institute, n.d.)

Brief Overview

This study is presented in five chapters. The first chapter has provided an introduction to cytoreductive surgery + hyperthermic intraperitoneal chemotherapy (CS+HIPEC), the constructs of quality of life (QOL) and sleep quality, and the importance of measuring these constructs in patients after treatment. Also provided is the purpose of the study, the statement of the problem, the research questions, the need for the study, and definitions of key terms. The second chapter contains a review of the literature related to CS+HIPEC, the QOL of patients post-CS+HIPEC, the sleep quality of adult cancer patients and survivors, as well as QOL and sleep quality assessment. The third chapter contains the methodology to be used in this study, including participants, sampling method, instruments and data analyses. The fourth chapter presents the results of this research according to each research question. Finally, the fifth chapter summarizes the study and includes limitations and recommendations for future research in the area of assessment of quality of life and sleep quality in patients who have received CS+HIPEC.

CHAPTER II

LITERATURE REVIEW

In 1884, in a desolate area now referred to as the upper West side of Central Park, construction began on the first cancer treatment center in the United States - The New York Cancer Hospital (Rowland, 1998). The pervasive belief of the time was that cancer was contagious, so this remote location was strategically chosen for purposes of isolation and the building was intentionally constructed to discourage the spread of hypothesized cancer-related germs between patients. The NY Cancer Hospital continued to house individuals with minimally understood and largely incurable diseases until 1948, when it was moved to an alternate location on the East side of NYC and renamed *Memorial Hospital for Cancer and Allied Diseases* (Rowland, 1998). Although the advent of antibiotics, anesthesia, and effective therapies was on the horizon (Rowland, 1998), doctors at this and a burgeoning number of other facilities commonly refrained from telling patients their respective diagnoses, as their prognoses and life expectancies remained grim. In 1960, this initial treatment facility with a growing number of patrons was once again renamed, acquiring the familiar title of *Memorial Sloan-Kettering Cancer Center*. Alongside subsequent medical discoveries and augmented technologies, this facility also steadily acquired the reputation of a renowned, state-of-the art comprehensive cancer research and treatment facility (Rowland, 1998). This impetus for growth and advancement within the field of cancer care was spurred by not only the high

prevalence of cancer within society but also the variety of diagnoses subsumed under the auspices of the cancer family that doctors routinely confronted.

Prevalence and Incidence Data

Cancer is defined as a sizeable number (approximately one hundred) of multifarious diseases that vary in nature (i.e. growth rate, invasiveness, prognosis, responsiveness to treatment and average age of onset) as a consequence of the cell type of primary origination (Klug, Cummings, Spencer, & Palladino, 2009). Despite these behavioral variations of members of the cancer family, these diseases all share some fundamental molecular properties that serve to place them under the auspices of the cancer family. Cell proliferation (or atypical cell growth and division) and metastasis (a process in which cancer cells spread to and subsequently invade other parts of the body) are the two underlying properties shared by all cancers (Klug et al., 2009). In healthy cells, genes regulate the rate and place of cell growth and division stringently. When genes become mutated or are expressed inaccurately, however, these processes can go awry, leading to unregulated cell proliferation and spread (Klug et al., 2009).

Cancer is precipitated by internal factors (including hormones, inherited conditions, metabolic-induced mutations, and immune conditions) and external carcinogens (including chemicals, radiation, tobacco, and infectious organisms, among many others) (American Cancer Society, 2009). A combination or sequence of any of the aforementioned may be sufficient to cause or maintain cancer. In the sense that genes control cell growth and division, all cancer is genetic. Only a small percentage (approximately 5%) of cancers is truly hereditary, however, being passed down through

generations (American Cancer Society, 2009). Most cancers develop following genetic damage incurred throughout one's lifetime. Typically, many errors in the DNA (the cell's genetic material) must occur prior to carcinogenesis, meaning cancer development is often a multistage process (American Cancer Society, 2009). If DNA damage is incurred prior to cell division, healthy cells will work to repair damage to the DNA sequence. Many individuals have accrued mutations, however, in sections of genes that regulate apoptosis (cell death), cell growth and cell repair. In these individuals, if the genetic material of the cell is not repaired prior to cell division, heritable mutations are passed on to daughter cells and more damaged cells may proliferate (American Cancer Society, 2009).

The risk of developing cancer increases with age, translating into the majority of cases occurring in middle-aged or older individuals (American Cancer Society, 2009). Approximately 77% of all cancers are diagnosed in individuals who are 55 years of age or older. The American Cancer Society defines one's lifetime cancer risk as the "probability that an individual, over the course of a lifetime, will develop or die from cancer" (American Cancer Society, 2009, p. 1). American men have almost a one in two lifetime risk of developing cancer, while the lifetime risk of American women is slightly higher than one in three. Relative risks, or the "measure of the strength of the relationship between risk factors and a particular cancer" (p. 1) also can be estimated. For example, a male who smokes is approximately 23 times more likely to develop lung cancer than a male who does not smoke tobacco (i.e. relative risk is 23). Inherited

conditions, lifestyle choices, and exposures all impact relative risks (American Cancer Society, 2009).

In January 2005, the National Cancer Institute estimated that approximately 11.1 million Americans who have received a diagnosis of cancer at some point in their lives were still living (American Cancer Society, 2009). The American Cancer Society estimates the diagnosis of 1,479,350 new cancer cases in 2009, excluding non-invasive carcinoma (except those involving the bladder), basal cell, or squamous cell skin cancers (American Cancer Society, 2009). The most frequent cancer diagnoses include lung and bronchus cancer (219,440 new cases in 2009, both sexes), breast cancer (194,280 new cases in 2009, both sexes), prostate cancer (192,280 new cases, males), and colon cancer (106,100 new cases in 2009, both sexes). Approximately 562,340 Americans are likely to die from their respective cancer diagnosis in 2009, equating to approximately 1,500 cancer-related deaths each day (American Cancer Society, 2009). These rates make cancer the second leading cause of death in Americans, second only to heart disease, accounting for approximately one out of every four U.S. deaths. The total cost of cancer in America in 2008, as estimated by the National Institutes of Health, was \$228.1 billion (i.e., \$93.2 billion in direct medical costs; \$18.8 billion in indirect costs, including loss of work productivity; and \$116.1 billion in indirect mortality-related costs, including loss of work productivity as a consequence of premature death) (American Cancer Society, 2009).

Cancer survival rates are extremely variable, given the type of cancer and diagnostic stage (American Cancer Society, 2009). Even with relative survival estimates

for specific cancer types, great individual variation is noted. Collectively, survival rates have improved greatly over time due to screenings and earlier diagnosing as well as enhanced treatments and technologies. Illustrating these trends in improved survival are the five-year survival rates across time for all diagnoses, increasing from 50% in 1975-77 to 66% in 1996-2004 (American Cancer Society, 2009).

Prevalence and Incidence of Peritoneal Carcinomatosis

Without the application of or access to augmented technologies and treatments, however, survival estimates often remain grim for individuals with certain diagnoses. For example, in a multicenter study of 370 individuals with peritoneal carcinomatosis, the mean and median survival times were 6.0 months and 3.1 months, respectively (Sadeghi et al., 2000). For individuals who do not seek treatment for peritoneal carcinomatosis, death comes quickly and often is preceded by many complications. Peritoneal carcinomatosis is common in individuals with certain primary diagnoses, including colon, rectum, ovary, stomach, and appendix cancer. The American Cancer Society anticipated 106,000 new colon cancer diagnoses, 21,130 stomach cancer diagnoses, 40,870 rectal cancer diagnoses, and 21,550 ovarian cancer diagnoses in 2009 (American Cancer Society, 2009). Of these, approximately 10-15% of the individuals who develop colorectal cancer in 2009 (Dawson, Russell, Tong, & Wisbeck, 1983; De Bree et al., 2004; Shen, Stewart, & Levine, 2009), 50% of those diagnosed with gastric cancer (Sugarbaker & Yonemura, 2000; Shen et al., 2009), and approximately 75% of those with ovarian cancer (Deraco, Respagliesi, & Kusamura, 2003; Shen et al., 2009) can anticipate having peritoneal dissemination.

Appropriate treatments targeting the primary diagnosis may prevent these peritoneal metastases in the first place. Shen et al., (2009) noted the potential for increased survival with the CS+HIPEC procedure for those who already have contained peritoneal metastases. Individuals with better performance statuses (i.e., The Eastern Cooperative Oncology Group standardized scores, ranging from zero (fully active and performing all pre-disease activities) to five (dead), that are assigned by the medical practitioner as an indicator of the general functional status of an oncology patient) (Oken et al., 1982) currently achieve a median survival of 21.7 months post-CS+HIPEC, while those with poorer performance statuses achieve a median survival of 9.5 months. Compared to the respective mean and median survival times for those with peritoneal metastases who do not pursue treatment (6.0 months and 3.1 months, respectively; Sadeghi et al., 2000), these estimates denote substantial extensions of life.

The review of the treatment- and disease-related challenges confronted by individuals who receive CS+HIPEC that follows provides the reader with an understanding of what patients actually endure in hopes of achieving these extensions of life. Specifically, a detailed overview of the anatomy and physiology of peritoneal metastases and the recommended surgical techniques and chemotherapeutic agents utilized for their treatment illustrates the physical demands encountered by these individuals.

Cytoreductive Surgery + Hyperthermic Intraperitoneal Chemotherapy (CS+HIPEC)

Sticca (2003) referred to the aggressive treatment of intra-abdominal malignancies as one of the remaining frontiers in oncology, presumably because of the high morbidity and mortality rates (Stewart, Shen, & Levine, 2008), the unproven and unaccepted benefits for some individuals with peritoneal carcinomatosis (Sticca, 2003), the small number of surgical oncology teams who routinely perform this procedure (Levine, 2004), and the inevitable death awaiting those who do not receive such treatment (Stewart et al., 2008). Certain surgical oncologists, however, are becoming more skilled and comfortable in performing this procedure. They are familiarizing themselves with the terrain, becoming more adept at selecting appropriate surgical candidates and ultimately offering some candidates the possibility of extended life (Stewart et al., 2008).

Peritoneal Metastases

Intimately involved in numerous bodily functions, including intestinal motility, breathing, and lymphatic and other bodily fluid circulatory exchange (Spratt, Edwards, Kubota, Lindberg, & Tseng, 1986), the peritoneum is the “serous membrane reflected over the viscera and lining the abdominal cavity” (Thomas, 1997, p. 1449). The mesothelium (or lining) of the peritoneum has many papilla, or projections, that serve to increase the total surface area of the peritoneum and enhance the rate of fluid diffusion (Spratt et al., 1986). The peritoneal cavity can be divided into the greater and lesser cavities, with the greater peritoneal cavity housing the majority of the abdominal viscera.

Within the greater peritoneal cavity, the visceral peritoneum protects and sustains the location of the viscera in its mesentery, or folds (Thomas, 1997). The parietal peritoneum lines both the pelvic and abdominal walls as well as the undersurface of the diaphragm (Thomas, 1997). Cells within the peritoneum secrete serous fluid that serves to moisten the surfaces of the abdominal organs, permitting them to slide along one another as the shape of the intestinal tract alters throughout the course of digestion and absorption (Thomas, 1997). The lesser peritoneal cavity has a frontal boundary that is bound to the back side of the stomach wall; the underside and left lateral margins are marked by the anterior side of the transverse mesocolon; the dorsal surface of the lesser peritoneal cavity is peritoneum that rests above the pancreas; while the right side boundary is the gastrohepatic ligament's medial border (Spratt et al., 1986).

Unfortunately, the peritoneal cavity, its mesothelial lining, and the viscera it surrounds are all susceptible to both primary and metastatic cancers (Spratt et al., 1986).

Numerous intra-abdominal malignancies may extend through the peritoneum (Stewart, Shen, & Levine, 2008), precipitating mucin-producing cells to spread throughout the peritoneal cavity, also known as peritoneal carcinomatosis (Sugarbaker, 1989). Specifically, this peritoneal carcinomatosis seems to occur in one of three distinct patterns: through direct extension from the primary origin, by means of the spread of tumor cells through the peritoneal fluid, and via trauma or surgical procedures (Stewart, Shen, & Levine, 2005). Secondary peritoneal involvement may have a variety of presentations (Spratt et al., 1986), which is determined by the extent of parietal or visceral peritoneum involvement, the characteristics of the primary tumor (e.g. colon,

appendix, ovary, etc), the extent to which alternate surrounding structures have been impacted, and whether lymphatic invasion has occurred (Spratt et al., 1986). Clinically, patients may present with pain, intestinal obstruction, or ascites (i.e., buildup of peritoneal fluid and obstruction of fluid outflow, ultimately leading to abdominal distension (Spratt et al., 1986; Thomas, 1997)), among others (Spratt et al., 1986).

Peritoneal carcinomatosis is most frequently found around the stomach and colon (Sugarbaker, 1989). Specifically, the omentum (a double fold of peritoneum that is attached to the stomach and other abdominal viscera and contains a cavity referred to as the omental bursa (Thomas, 1997)) often is heavily involved, creating an *omental cake* of tumor that is typically attached to the stomach and colon (Sugarbaker, 1989). Following stomach and colon involvement, the pelvic peritoneum is most frequently affected. The undersurfaces of the hemidiaphragm, the right suprahepatic space between the liver and diaphragm, the undersurface of the liver, and many other areas within the peritoneal cavity are commonly encased in tumor, resulting in single masses of organs (Sugarbaker, 1989). Interestingly, with the exception of two anatomic sites that are relatively immobile, most small bowel surfaces remain free of tumor metastasis, presumably due to the peristalsis movements (Sugarbaker, 1989).

Individuals with peritoneal metastases from differing primary origins can anticipate different disease experiences and outcomes based on, among other things, the histopathology of the primary disease itself, the potential for distant metastases, and the presence or absence of genetic mutations within the host (Sticca, 2003). Sticca (2003) noted the accumulation of evidence for the success of CS+HIPEC in the presence of low-

grade peritoneal malignancies, in which the odds of dissemination of disease to the outside of the peritoneal cavity are low. Such an example of a low-grade malignancy is pseudomyxoma peritonei (PMP). In fact, CS+HIPEC is now considered the “standard of care in these low-grade malignancies, converting a once uniformly fatal condition to a readily curable disease (greater than 75% long-term survival in some series)” (Sticca, 2003, p. 484). By contrast, colonic adenocarcinoma is considered a moderate to high-grade tumor, making long-term disease-free survival less probable (Sugarbaker, 1989). Colonic adenocarcinoma is more invasive, making its surgical removal more difficult. Although it rarely spreads through blood or lymph channels, colonic adenocarcinoma will invade the intra-abdominal structures and implant itself on a plethora of surfaces within the peritoneal cavity (Sugarbaker, 1989). Likewise, its residual tumor is more solid and has more advanced vasculature, making it more adept at removing chemotherapeutic agents via capillary networks and lymphatic channels (Sugarbaker, 1989) and equating to less tumor penetration by the respective chemotherapeutic agent. These characteristic differences in tumor grade should be taken into treatment consideration.

Rationale for CS+HIPEC

Without treatment, peritoneal carcinomatosis is a homogeneously fatal disease, bearing a median survival of six months (Stewart et al., 2008). Without intervention, hosts will experience bowel obstruction, poor intestinal function, and/or ascites, quickly followed by subsequent death (Spratt et al., 1986; Stewart et al., 2005; Stewart et al., 2008). Until recently, this aforementioned fate was inevitable (Sticca, 2003). The use of systemic chemotherapy agents for peritoneal carcinomatosis is palliative in nature,

yielding little, if any, extension in survival (Stewart et al., 2008). Chemotherapeutics administered systemically demonstrate poor penetration of tumors within the peritoneal cavity (Stewart et al., 2005; Sticca, 2003), largely because of the peritoneal-plasma partition. Likewise, any drug given orally or intravenously arrives at the tumor through the circulatory system, all-the-while being diluted by the vascular pool and ultimately reaching these drug-resistant tumors at a diluted dose (Spratt et al., 1986). The presence of other healthy corporeal tissues and organs limits higher drug dose possibilities and therefore potential effectiveness on drug-resistant tumors (Spratt et al., 1986). That is, the patient experiences the toxicity of systemic chemotherapy administration with little benefit in return. Similarly, cytoreductive surgery alone may effectively remove macroscopic disease from the peritoneal cavity and reduce symptom burden, yet these benefits are only temporary. Residual microscopic disease inevitably remains and will continue to grow (Stewart et al., 2008). These options, then, do not offer the individual significant survival benefits and actually carry many potentially severe side effects.

If peritoneal metastases are localized, and distant metastases are non-existent, the disease is considered locoregional, warranting consideration of corresponding aggressive locoregional approaches, such as CS+HIPEC (Sticca, 2003; Stewart et al., 2008).

Cytoreductive surgery is used to resect involved viscera (e.g. hysterectomy, splenectomy, oophorectomy, large/small bowel resection) and gross tumor within the peritoneal cavity (Stewart et al., 2008). Stewart, et al. (2008) noted the constant correlation between the completeness of the CS and survival, indicating survival is positively correlated with the amount of macroscopic disease that the surgeon is able to remove. This resection is

essential, as the chemotherapeutic drugs are only able to penetrate disease a few millimeters (Stewart et al., 2004). If only small amounts of microscopic disease remain, the localized chemotherapy perfusion should reach the remaining residual disease and overcome these drug-resistant cancers (Spratt et al., 1986; Stewart et al. 2008).

Verwaal et al. (2003) randomized 105 individuals with peritoneal carcinomatosis of a colorectal origin to standard treatment (i.e., systemic chemotherapy) or experimental treatment (i.e., CS+HIPEC). Verwaal reported a median survival of 12.6 months for the standard treatment individuals and 22.3 months for the experimental treatment individuals ($p = 0.032$), suggesting a significant difference in survival time between treatments. The mortality rate of the experimental group, however, was eight percent. Experimental individuals who had a complete cytoreduction of no more than five of the seven abdominal regions involved by tumor at the time of surgery fared better in terms of survival. Verwaal concluded that CS+HIPEC significantly improves survival estimates for patients with peritoneal carcinomatosis of colorectal origin, yet only if complete cytoreduction is attainable or no more than five out of the seven abdominal regions are involved by tumor.

Utilizing this procedure, then, specialized and experienced surgical oncologists who wisely select their surgical candidates have been able to give individuals with peritoneal metastases long-term survival (Stewart et al., 2008). Despite this success, Levine (2004) noted that the “operative procedures attendant to aggressive cytoreduction are lengthy and challenging, associated with morbidity, and utilize a great deal of hospital, blood bank, and house officer resources” (p. 351). For these reasons, there are

less than 25 active centers with individuals who perform this procedure within the United States, and an even smaller number with experience in treating over 100 cases (Levine, 2004).

Cytoreductive Surgery

Given that a positive correlation exists between completeness of cytoreduction and survival (Stewart et al., 2008), the goal of CS should be the complete removal of all macroscopic disease and the opening of all abdominal adhesions (Sugarbaker, 1989) rather than partial debulking. Good surgical candidates, then, are those who are medically and emotionally fit to undergo the extensive CS (i.e., good performance status) and who have disease that is localized and considered completely or significantly resectable (Stewart et al., 2008). Pre-operative imaging permits surgeons to judge an individual's candidacy for surgery, plan operative techniques, and spare individuals with extra-peritoneal disease from unnecessary surgery (Stewart et al., 2004). These operative images do have their limitations, however, especially relative to disease within the peritoneal and pelvic cavities (Stewart et al., 2004). More disease than anticipated may be present once an individual's cavity is opened for exploration, often to the extent that the planned chemotherapeutic perfusion post-surgery is aborted.

In the operation room, a large midline incision is performed for the surgical exploration (Stewart et al., 2004). The surgeon enters the peritoneal cavity with the intent to remove all gross tumor from the visceral and peritoneal surfaces, usually with ball-tipped electrocautery on pure cut and high voltage (Sugarbaker, 1989). Strong traction exists between healthy and tumor tissue, and, using such an instrument, the

surgeon is able to remove strictly the tumor and affected surfaces of the peritoneum, ultimately leaving the underlying viscera, healthy tissue and fat in adequate shape (Sugarbaker, 1989). Great care and skill must be utilized around structures with high amounts of collagen (e.g. ureters, large blood vessels), as severe damage may be incurred. Irrigation with cool water is often utilized during the procedure to protect these structures (Sugarbaker, 1989). Additionally, great care must be taken around the diaphragmatic muscle, as perforations or certain types of contact may precipitate diaphragmatic contractions (Sugarbaker, 1989). Expert levels of knowledge and experience as well as great familiarity with surgical tools, then, are requisites. Sugarbaker (1989) listed the advantages of using ball-tipped electrocautery for such a procedure, including its speed and precision of dissection, its ability to clearly hit a line of dissection between tumor and healthy tissue, and the hefty amounts of tumor it permits the surgeon to remove in one procedure without the great amount of blood loss one might anticipate from dissection. A laser smoke evacuator also is commonly used to remove particles, smoke and odor from the surgical space (Sugarbaker, 1989).

If significant tumor burden is present, removal of involved viscera (e.g. spleen, ovaries, uterus, etc.) and the stripping of the peritoneum from the abdominal wall are necessary (Stewart, et al., 2008). If essential organs are affected by tumor burden, electrocautery will then be utilized so that they may be left within the host. Next, anastomoses (i.e. the surgical connection of two tubular structures (Thomas, 1997)) will be completed prior to or following the HIPEC as needed. If an ostomy (i.e., surgically formed, artificial exit sites leading from the intestine or bowel to the outside of the body)

(Thomas, 1997) is needed, the surgeon will perform the procedure following the perfusion of chemotherapy (Stewart et al., 2008). A cytoreduction classification scheme based on the amount of gross disease and microscopic margins remaining is the utilized so that a uniform grading system of the surgical component of the procedure is in place (Stewart et al., 2008).

Following the removal of as much macroscopic disease as possible, catheters are placed through the abdominal wall, to the side of the rectus muscles, and sutured at the peritoneal level (Sugarbaker, 1989). The abdominal cavity is then flushed with a solution that contains antibiotics. The solution also serves to remove remnant tissue and blood and prevent infection and the formation of adhesions (Sugarbaker, 1989). Prior to closing the abdominal cavity, remaining debris that could potentially clog the catheters (e.g. tissue) must be removed, and a cessation of bleeding should be achieved. Drains are placed in the lower flank for subsequent fluid removal (Sugarbaker, 1989).

Intraperitoneal Chemotherapy

No matter how complete the CS, surgery alone will not remove all microscopic and residual peritoneal disease. Without the utilization of chemotherapeutics to attack the residual disease, recurrent peritoneal carcinomatosis is inevitable, and long-term survival is unrealistic (Sugarbaker, 1989). Attempting to overcome drug-resistant tumors that would require dangerous or impractical cytotoxic agent dosages or administration schedules if administered orally or intravenously, doctors of the 1970's began investigating with the peritoneal perfusion of cytotoxic agents to target localized disease (Spratt et al., 1986).

With the largest surface area of any serous membrane in the human body, the peritoneum has an extensive absorptive area consisting of a vast capillary and lymphatic network (Spratt et al., 1986). Optimal drugs for HIPEC, then, are those that are not quickly absorbed from the cavity, such that high concentrations of the drug remain in the vicinity of the tumor (Spratt et al., 1986). Levine et al. (2008) noted that these are typically drugs with high molecular weights that do not generally dissolve in lipids. By utilizing indwelling catheters, doctors have been able to achieve high concentrations of such drugs in the cavity yet low levels of these agents systemically (Spratt et al., 1986). These drugs ideally should be administered in large volumes of fluid so that the abdomen is distended and the drugs reach all cavity areas (Sugarbaker, 1989). Spratt et al. (1986) listed numerous desirable characteristics of drugs and the peritoneal drug delivery environment, including tumors with small diameters that are confined to the surface of the peritoneum, an abdomen cleared of obstructions or adhesions so that drug circulation within the cavity is unobstructed, utilization of a drug that is slow to be absorbed by the peritoneum yet readily clears the peritoneal plasma membrane, and drugs that are quickly cleared and excreted from systemic circulation. Either an open (i.e., covering the abdomen with a plastic sheet while administering chemotherapy) or closed (i.e., surgically closing the abdominal cavity while administering chemotherapy) technique can be utilized for the administration of the chemotherapy (Stewart et al., 2005). Proponents exist for both techniques.

In addition to better understanding the optimal means of drug administration for these tumors, researchers also learned the importance of timing relative to this procedure.

Considering these drugs attack tumor by means of diffusion, tumor cells on the surface of the peritoneum or free floating inside the cavity are exposed to the most potent levels of drugs (Spratt et al., 1986). With subsequent layers of tumor, however, the drug becomes less potent and therefore less effective. Only capable of penetrating microscopic disease a few millimeters, chemotherapeutic perfusion should occur when gross tumor has been removed and adhesions have been opened (Stewart et al., 2008). Such a corporeal environment exists during CS, with all peritoneal surfaces exposed (Levine et al., 2007). Sugarbaker (1989) stated intraperitoneal drugs should be administered within the first five post-operative days, prior to the formation of post-operative adhesions that may prevent optimal drug diffusion.

In addition to issues related to mode and timing of administration, a rationale for hyperthermia in the context of the drugs was suggested. Specifically, hyperthermia has a synergistic effect on chemotherapeutic agents, making them more potent than if utilized in a non-heated form (Stewart et al., 2008). Mitomycin-C (MMC) is the most commonly used drug for intraperitoneal chemotherapy at this time, although other agents are utilized and being explored (Stewart et al., 2008). Spratt et al. (1986) noted that fluids that are 42-50 degrees Celsius are tolerated relatively well, incurring minimal damage to healthy tissues. After 30 hours of exposure to fluids that are 42 degrees Celsius, three to four hours of exposure to fluids that are 45 degrees Celsius, or after minutes of exposure to fluids that are warmed to 50 degrees Celsius, neoplasms will experience a thermal death (Spratt et al., 1986). The utilization of heated drugs, then, may maximize results.

CS+HIPEC at Wake Forest University Baptist Medical Center. A review of the intricacies of this procedure performed by the surgeons at WFUMBC demonstrates how all of the previously reviewed steps are combined and provide clarity about the medical procedures received by study participants (all of whom received CS+HIPEC at WFUMBC), as specifics of the procedure may differ between institutions. The surgical oncologists at WFUBMC utilize a closed (as opposed to open) technique, reasoning the closure of the abdominal cavity during perfusion will result in more effective chemotherapy penetration and will concurrently result in less exposure of the team to the toxic agents while in the operating suite (Stewart et al., 2005). Patients are passively cooled to 34-35 degrees Celsius throughout cytoreduction, during which the peritoneum is stripped of the abdominal wall and any non-vital viscera with tumor burden are removed. Following complete cytoreduction, perfusion catheters with temperature probes are placed through the skin. Under the left and right hemidiaphragms are two inflow catheters, while outflow catheters with drainage bulbs are positioned in the pelvis (Stewart et al., 2005). The main abdominal incision is then temporarily sutured so as to prevent leakage of the perfusate. A perfusionist establishes a perfusion circuit with approximately three Liters of solution flowing at an approximate rate of 800 to 1000 mL per minute (Stewart et al., 2005). To further enhance drug distribution, the abdomen is gently massaged throughout the perfusion. A roller pump and heat exchanger are used to continuously move the fluid and maintain the desired temperature. The inflow temperature is not permitted to exceed 42.5 degrees Celsius, while an outflow temperature of 40 degrees Celsius is sought (Stewart et al., 2005). When outflow

temperatures climb above 39 degrees Celsius, 30 mg of MMC is added to the solution. After approximately one hour, another ten mg of MMC is added so as to maintain dosage concentrations (Stewart et al., 2005). The total perfusion time with MMC is approximately two hours. Following completion of the perfusion, the cavity is rinsed with approximately two to three Liters of Ringer's solution and passively drained (Stewart et al., 2005). The incision is once again opened and catheters are removed. Anastomoses are created as needed, and a final inspection of the abdomen occurs. The patient is then surgically closed, and any necessary procedures (e.g. ostomies) are completed. Finally, patients are transplanted to the post-anesthesia care unit and subsequently the intensive care unit (Stewart et al., 2005).

In a review of their experience with 501 procedures, Levine et al. (2007) offered their surgical statistics with patients from WFUBMC. Of these 501 procedures, 460 procedures were on patients receiving their first CS+HIPEC; 37 were receiving their second CS+HIPEC; and four were receiving their third treatment. Influenced largely by the location and extent of the disease, the mean operating time was 560 minutes (+/- 175 minutes; range 250-1080 minutes). The median days in the intensive care unit and hospital were two and nine days, respectively, while the mean hospital stay was 15.3 days (+/-17.9 days). The surgeons listed 13 primary sites of origin, in addition to one "other" category. Of the primary sites, appendix (35.4%), colon/rectum (28.9%), ovary (10%), and stomach (9.1%) were the most common. In addition to the peritoneal resections, Levine et al. (2007) also listed 16 potential organs of resection and the percentage of individuals who lost the respective organ. Most commonly resected organs in these 501

procedures included omentum (59.1%), colon (42.9%), small bowel (35.1%), spleen (33.1%), and gallbladder (17.8%). A total of 20.1% of patients received ostomies. The 30-day morbidity and mortality rates were 43.1% and 4.39%, respectively (Levine et al., 2007). The most common post-operative complications included pneumonia, hematologic toxicity, sepsis, respiratory failure, wound infection, anastomotic leak, and enterocutaneous fistula. Finally, Levine et al. (2007) found significant differences in survival based on primary site of origin ($p = 0.0001$): colorectal (16.4 months), appendix (63.5 months), gastric (6.1 months), mesothelioma (27.1 months), sarcoma (28.1 months), ovarian (28.5 months). The overall median survival rate was 22.2 months, while the overall survival rates at one, three, and five years were 66.8%, 40.0%, and 27.8% (Levine et al., 2007).

Factors Associated with Success

The survival rates based on primary site of origin provided by Levine et al. (2007) demonstrate significant variability, suggesting some candidates will have a longer predicted survival period than others. In addition to primary tumor site, alternate factors likely impact survival and surgical success rates, including the completeness of the cytoreduction, regardless of the primary diagnosis (Levine et al., 2007). Additionally, the level of skill, experience and knowledge possessed by the respective surgical team seems to play a large role. Levine et al. (2008) and Smeek, Verwaal, and Zoetmulder (2006) suggested the presence of a steep learning curve, involving not only improvement in techniques over time but also better candidate selection with more operating experience. Stewart et al. (2005) revealed the following selection criteria that are utilized at

WFUBMC: the prospective candidate must be medically fit to undergo the extensive CS+HIPEC; extra-abdominal disease cannot be present; the surgeon must deem the peritoneal carcinomatosis completely or substantially resectable; parenchymal hepatic metastases cannot exist; and bulk retroperitoneal disease cannot be present. These stringent selection criteria are essential so that disruptive, invasive surgical procedures are not performed on individuals who will not benefit substantially or who are in the palliative stages of life. At the same time, however, Stewart et al. (2005) noted, “only a handful of patients who are potential candidates for this therapy actually receive it, and this is underscored by the relatively small number of patients accrued to phase II studies even at large ‘perfusion centers’” (p. 773). Many more individuals with peritoneal metastases, then, could have a chance for long-term survival with this procedure. Finally, McQuellon and Duckworth (2009) suggested the importance of incorporating ongoing QOL assessment throughout the trajectory of this experience so that correlate psychosocial issues do not go unaddressed. A biopsychosocial approach encourages this multidimensional care.

Risks and Toxicity

CS+HIPEC offers individuals with peritoneal metastases the possibility of achieving long-term survival when such a possibility would not exist otherwise. Unfortunately, on numerous occasions, these results are not achieved altogether or are not achieved without substantial cost in the form of morbidity (Sugarbaker, 1989) and temporary reductions in QOL. With a post-procedure median estimated survival time of less than two years (Levine et al., 2007), patients and their loved ones must decide

whether the potential benefits outweigh the potential costs, given their respective conditions. Levine et al. (2007) advocated for detailed pre-operative discussions with prospective patients and families so that every prospective candidate is truly an informed consumer. Morbidity and mortality rates as well as psychosocial considerations should all be important topics of discussion in these talks.

Complications are common with this extensive procedure, and death is certainly a realistic occurrence as well (Sugarbaker, 1989). After reviewing reports from centers with surgical teams who perform CS+HIPEC, Stewart et al. (2008) reported that post-procedure morbidity rates are high, ranging from 27-56%, while mortality rates range from 0-11%. Often, a grading system is implemented to rate the severity of these complications and to provide the surgeons with a systematic means of recording the extent of the complications experienced by their patients (e.g., I- a diagnosable problem that does not require treatment; II- a complication warranting medical intervention; III- a problem with potentially severe ramifications yet was resolved conservatively with medical intervention; IV- a problem warranting emergency intervention, typically in the form of surgery or regression to the ICU; V- death) (Sugarbaker et al., 2006). Likewise, complications may be categorized by means of their association with various aspects of the procedure itself (e.g., the invasive surgical procedure, catheter-related, the localized concentration of the drugs, systemic toxicity, etc) (Spratt et al., 1986). Regardless of the classification scheme, the morbidity rates relative to this procedure are high, thereby making the acute recovery stage complicated and lengthy hospitalizations, often far from home, commonplace.

For instance, in their review of 103 consecutive CS+HIPEC procedures on patients in Sweden, van Leeuwen, Graf, Pahlman, and Mahteme (2008) reported a 56.3% morbidity rate and the death of one patient post-procedure. Of those who had complications, respiratory concerns, abscesses, systemic sepsis, neutropenia, urinary tract infections, and small bowel fistulas were the most frequent. Approximately one third of these 103 individuals required additional surgical or invasive procedures to correct their complications (van Leeuwen et al., 2008). Smeek et al. (2006) also reported a high complication rate, including a 54% toxicity rate and a surgical complication rate of 38%. Primary complications in these individuals included perforations or suture leaks of the small bowel, gastrointestinal fistulas and abscesses. Sugarbaker et al. (2006) reviewed their own morbidity and mortality rates following 356 procedures and revealed a 2.0% 30-day post-procedure mortality rate (i.e. seven persons). One hundred and forty three patients, with line sepsis, urinary tract infections and insufficient hemoglobin levels occurring frequently, experienced one or more grade III complications. One or more grade IV events occurred in 67 patients and included hematological, cardiovascular and gastrointestinal complications. For 11.2% of these patients, a return to the operating room was required on account of anastomotic leaks, post-operative bleeding and fistulas, among others (Sugarbaker et al., 2006). These statistics shared by surgical teams with extensive experience with this procedure demonstrate both the frequency and gravity of some of these complications. If offered the possibility of extended life, however, many patients are willing to take the risk and endure such morbidities.

Many surgeons report correlations between the number of morbidities experienced post-operatively and the patient's stage of carcinomatosis, the length of the operation, and the number of anastomoses performed (Stewart et al., 2008). Spratt et al. (1986) also noted the negative correlation between a surgeon's experience with the procedure and the number of complications, again suggesting the presence of a steep learning curve and the need to select the respective surgical team sagely. Although most patients proceed to recover from their complications, most will eventually die from recurrent disease (Stewart et al., 2008). Additionally, many will never return to or attain their desired level of physical functioning and well being (McQuellon & Duckworth, 2009). These possibilities may combine to make this surgical decision difficult.

Although many hurdles and complications are possible, with CS+HIPEC, surgical oncologists are able to offer individuals with peritoneal metastases the possibility of achieving extended life. With this possibility for extended life, however, comes a concurrent need to study the *quality* of their survivorship and whether the costs of the procedure are justified in the minds of its patrons. In summary, the appearance of a sufficient number of survivors within a cancer diagnostic or treatment group is the essential and precipitating factor for the commencement of survivorship studies within that respective population, and the number of individuals who have had CS+HIPEC for peritoneal metastases continues to increase.

Survivorship in Oncology

The aforementioned story behind the growth and transformation of Memorial Sloan-Kettering Cancer Center in many ways parallels the story of American society's

perception and regard of a cancer diagnosis and the study of survivorship issues in cancer care. In the early 1900's, patients were often "humanely" spared from hearing their diagnosis, as such a diagnosis was, more often than not, equated with an untimely and disfiguring death (Rowland, 1998). Therefore, secrecy, isolation, and social stigma encircled the lives of those diagnosed with this disease. With enhanced understanding of the disease coupled with medical advances in anti-microbial and disease fighting agents, however, oncology clinicians began experiencing some successes relative to extending patients' lives.

Specifically, doctors' first curative successes occurred within the pediatric oncology arena, preventing central nervous system relapse in children with Acute Lymphoblastic Leukemia (ALL) (Ganz, 2003; Rowland, 1998). Since ALL is the most prevalent form of childhood cancer, the ramifications of curative possibilities were quickly recognized. Prior to this advent, cancer survivors simply did not exist in sufficient numbers to warrant attention to or research of survivorship issues in cancer patients (Rowland, 1998). Yet, alongside these medical advances, a new concept was being integrated into the cancer lexicon and experience- that of survivorship. Following the ALL breakthroughs, medical researchers began moving beyond strictly curative efforts to consider the quality of life post-treatment (Rowland, 1998).

This emphasis on life following treatment, and even life following cancer for many fortunate individuals, has continued to expand over time. In 1985, Fitzhugh Mullan detailed his personal cancer journey and survivorship issues in a writing entitled, "Seasons of Survival" (Mullan, 1985). The following year, he and a group of other

advocates established the National Coalition for Cancer Survivorship (NCCS). As a first order of business, these progressive thinkers challenged the current definition and concept of a survivor, at that time conceptualized strictly as a person who remains free of disease five years following her or his diagnosis (Rowland, 1998). Recognizing that survivorship issues commence at diagnosis and take varying forms throughout the remainder of life, the NCCS members argued that an individual diagnosed with cancer should be able to consider and refer to her or himself as a “survivor” from the point of diagnosis and for the remainder of her or his life, regardless of the cause of death (Rowland, 1998). This broader, more encompassing concept of a survivor gave credence to the unique concerns confronted by persons with cancer from the moment of their diagnosis and began to inform thinking and research within the U.S. Consequently, the field of psychosocial oncology developed to train researchers and clinicians who have the requisite combination of drive, skills, ethic, and vision to serve this population and advance the understanding of survivorship issues.

Survivorship Research

Attention to survivorship and health outcomes relative to cancer care is essential for numerous reasons. For starters, a growing number of individuals are being diagnosed with cancer. Specifically, the aging of the population translates to a growing number of elderly persons who will be diagnosed with cancer, making research related to health outcomes pertinent for a larger number of people (Ganz, 2003). A major goal of survivorship researchers is to better understand the holistic impact of therapies, maximizing potential for cure and minimizing negative health effects (Rowland, 1998).

If numerous treatment options are available and patients have preferences for some toxicities over others, research on survivorship and health outcomes should inform decision-making (Ganz, 2003). Accurate information on primary treatments, their respective short- and long-term effects and any interactions between treatment-related effects and existing medical and mental health conditions is therefore essential.

Unfortunately, most of our research and current knowledge of treatment effects pertains to the acute and immediate effects of treatment rather than the long-term effects (Ganz, 2003), and less is known relative to treatment-related morbidity and interactions with comorbid conditions. Some patients may be accepting of any late effects of treatment simply because the associated therapy gives them the possibility of extended life; others may be less amenable to impaired functioning (Ganz, 2003) and may therefore want as much information as possible to decide whether to enter treatment in the first place. Regardless of patient preference, treatment-related decision-making should be informed by sound research, and any accumulated research should be incorporated into decision-making and systematic assessment following treatment (Ganz, 2003). Sound research also should serve as the basis of creation and implementation of evidence-based interventions that encourage healthy mental and physical adaptation (Rowland, 1998).

Reflecting on the growth and development of survivorship issues, many trends within the research are evident (Rowland, 1998). Broadly speaking, researchers have moved from strictly descriptive studies to intervention studies, from small cohort studies to large, multi-institutional studies following international cohorts over time, from

examining purely observable symptoms to researching mind-body impacts of drugs and interventions (Rowland, 1998). Although reviewing all of the trends is beyond the scope of this dissertation, it is important to highlight the existence of these trends and remaining gaps in need of researchers' attention. Specifically, Rowland (1998) noted the paucity of information related to underrepresented cancer sites and treatments (e.g. individuals with peritoneal metastases who have had CS+HIPEC) as well as individuals from low income, low education, ethnoculturally diverse, and rural backgrounds. Similar to survivorship issues in general, survivorship issues relative to specific diagnoses or novel treatments are not as salient until a sufficient number of persons begin surviving the disease or treatment, respectively. Researchers studying specific groups of survivors previously underrepresented within the literature on account of poor prognoses must work within that defined population and not make inferences beyond that sub-population (Ganz, 2003). In other words, as survivorship research progresses, the health outcomes of a potential array of diagnoses and novel treatments and their interactions with pre-existing characteristics and conditions may lead to unique post-treatment outcomes that warrant individualized research.

Quality of Life as an Outcome Measure

While studying survivorship issues within specific cancer or treatment-related populations, researchers may utilize a number of outcome measures, including some that are patient-rated in nature (Rowland, 1998). As medicine has become more patient-centered and patients have steadily become collaborative partners in their own health, such subjective, patient-rated measures have gained value and utility (Travado, 2006),

permitting the health team insight into the subjective world of the patient and her or his personal tolerance of its quality. One example of a patient-based outcome measure is quality of life assessment.

Rather than an altogether novel construct, QOL is a fresh referent for the longstanding concept of *general welfare* (Cella & Tulsky, 1993). References to this early QOL predecessor are apparent in the Declaration of Independence (i.e., the entitlement to seek happiness) and in the Preamble to the Constitution (i.e., the advancement of the general welfare of citizens), providing evidence for the existence of a similar construct throughout time (Cella & Tulsky, 1993). Definitions and measurement strategies of this evolving construct have taken different forms, often reflecting the zeitgeist, or spirit of the time. In the Great Depression, for example, QOL often was determined by means of finances and the possession of objects (Cella & Tulsky, 1993). As the 1960's approached (e.g. President Johnson's Great Society), the fluid definition of QOL began taking a more subjective, intrinsically-driven form, rather than an objective (i.e. possession of goods), form. With this morphing of the construct came a need for researchers to obtain subjective, patient-reported inputs and a simultaneous concern about the reliability of this subjective data (Cella & Tulsky, 1993).

To this day, many continue to hold that an individual's quality of life is, as a construct, extremely difficult to measure, with some even arguing that it is an intangible construct altogether (Rowland, 1998). Undoubtedly, many factors coalesce to impact one's perception of quality of life, and the relative merit each person gives to these factors often varies (Cella & Tulsky, 1993). Confusion also remains as to whether the

overall goal is to measure QOL or health-related quality of life (HRQOL), that is, QOL as a whole or QOL strictly as it pertains to cancer-related health. The often interchangeable use of these two terms causes discrepancies relative to what is actually being measured and how to interpret results.

Additionally, Roland (1998) noted the inherent difficulty of accurately measuring the QOL of cancer patients over time. Specifically, the adaptive nature of human beings often results in what is referred to as a *response shift*. With response shift, humans become less distressed by something that was initially distressing or disabling, as they make accommodations or alter their expectations. The respective stressor(s) or symptom(s) impairing QOL might continue to exist in the same, or an even more potent, form, yet individuals have accommodated and therefore rate their QOL as better than before (Rowland, 1998). These response shifts make the interpretation of the recovery trajectory and QOL difficult to ascertain. Finally, the differing perspectives of patients, mental health practitioners and physicians relative to the importance and weight of the scores as well as how to incorporate them into individualized health plans differs (Travado, 2006).

Despite these and other challenges related to QOL measurement and interpretation, countless researchers still hold that it is a construct of great importance, and patients and patient advocacy organizations demand continued attention to the psychosocial needs of patients (Travado, 2006). The existence of this construct in cancer care alone serves as a reminder of how far we have progressed in cancer care since the days of measuring success in the crude categories of death, cure, or disability

(Langenhoff, Krabbe, Wobbes, & Ruers, 2001). Gathering QOL information allows the health care team to gain access to needs that might have otherwise remained unknown or unacknowledged (Davies, 2009). Physicians and patients often have differing priorities (Halyard & Estwing Ferrans, 2008), and QOL data serves to underscore the subjective impact of a diagnosis or treatment alongside the observable, objective response. Some researchers have even demonstrated the predictive power of QOL scores relative to patient survival and response to treatment (Halyard et al., 2008). This type of estimated response gleaned through QOL scores becomes even more salient in a palliative setting, when patients have limited life expectancies and quality of life should be of the utmost importance (Langenhoff et al., 2001). Some researchers are interested precisely in this type of cost-benefit analysis of treatments, in the incorporation and estimation of adjusted *quality* years gained as a consequence of treatments. In the future, they envision more integration and use of these utility figures that integrate morbidity and mortality estimates with QOL data, resulting in estimates such as quality-adjusted life years (QALYs) or quality-adjusted time without symptoms of disease and toxicity of treatment (Q-TWIST) (Langenhoff et al., 2001). Although many future developments are needed in the practical application of such analyses, the future emphasis on considerations of quality in the context of cancer care is evident. In the art of comprehensive care, where patients' holistic well-being is the focus of attention and patients are increasingly becoming collaborative partners in their own care, acceptable QOL should be one of many outcome measures of interest (Langenhoff et al., 2001).

Langenhoff et al. (2001) pointed out the numerous definitions of QOL within the literature and argued there is no “best” definition when it comes to QOL. For example, The World Health Organization defined QOL as “individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns,” thereby reflecting the construct’s subjective nature and the relative importance of an individual’s cultural, environmental and social systems (*WHOQOL User Manual*, 1998, para. 5). As noted in the previous chapter, Cella and Cherin (1988) defined QOL as “patients’ appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal” (p. 70). Numerous variations in QOL definitions exist, with differing levels of specificity, yet most researchers concur that the construct of QOL and its respective measurement should be multidimensional, subjective (i.e. patient-rated), responsive to change over time (Langenhoff et al., 2001), and dual-sided in nature, incorporating negative aspects of the disease and treatment effects as well as positive life aspects, such as well-being (Cella & Cherin, 1988).

The precise number of principal aspects or domains composing QOL is, again, a subject of debate. Langenhoff et al (2001) stated that the consensus within the field is that the construct of QOL has three principal domains (i.e. physical, psychological, and social) plus a global assessment that yields information about the participant’s appraisal of her or his overall QOL. Rowland (1998), on the other hand, argued that QOL encompasses a minimum of four primary areas of importance. At its core, according to Rowland (1998), QOL includes a physical component (i.e. physical health and

symptoms), an emotional component (i.e. one's mood as well as cognitive and affective status), a functional component (i.e. one's ability to engage in daily living activities) and a social component (i.e. support, role functioning and financial burden) (Rowland, 1998). These aforementioned discrepancies in definitions and number of domains within the construct are highlighted throughout the various QOL instruments as well. Ultimately, the goals of the research should guide definition and instrument selection (Langenhoff et al., 2001).

In general, three categories of QOL instruments exist, and instrument selection, again, depends on the respective research goals (Langenhoff et al., 2001) and intended use of the acquired QOL data. QOL instruments may be classified as generic, cancer general or cancer disease-specific (Lipscomb, Snyder, & Gotay, 2007). Designed for use with an array of diseases and medical treatments, generic QOL instruments permit comparisons across varying treatments and conditions. It is precisely this generic quality and lack of specificity, however, which may make them less sensitive to some of the clinically relevant and unique aspects of a subgroup's experience (Langenhoff et al., 2001). Similarly, cancer general QOL instruments are generic in nature but have a narrower focus of strictly oncologic diseases. Disease-specific QOL instruments, on the contrary, were developed with a unique diagnostic or treatment-group's experiences in mind. They include domains that are particularly salient to the respective subgroup and may be designed to be more sensitive to changes within these domains (Langenhoff et al., 2001).

If relatively little is known about the QOL of a subgroup, a disease-specific measure has yet to be developed, or norm-based comparisons are of particular interest, a generic QOL instrument may be the best choice. If a valid and reliable disease-specific measure exists for the subgroup of interest and a detailed profile of salient QOL impairments for this respective population is of interest, the disease specific measure is the likely choice. Many researchers who have both categories of QOL instruments at their disposal may use a combination of the two categories (Langenhoff et al., 2001) so that both group comparisons and a detailed profile of the subgroup of interest are possible. Ultimately, no one instrument is the “gold standard”, fitting all conditions for all disease and treatment groups (Langenhoff et al., 2001). Research goals must guide instrument selection.

Despite the lack of agreement on a “best” definition of QOL and the varied number of hypothesized domains, all QOL instruments should meet certain standards. The U.S. National Cancer Institute created the Cancer Outcomes Measurement Working Group (COMWG) in 2001 with the goals of evaluating and progressing patient-rated outcome measurement (HRQOL in particular) (Lipscomb et al., 2007). The COMWG, in turn, adopted revised Medical Outcome Trust (MOT) criteria to evaluate QOL instruments. Adhering to MOT evaluation criteria, COMWG evaluators examine the following underpinnings of any QOL instrument to gauge its relative strengths and weaknesses: the conceptual and measurement model, reliability, validity, responsiveness, interpretability, burden/alternative modes of administration, and cultural and language adaptations (Lipscomb et al., 2007).

The *conceptual model* should underscore the selection of concepts, domains and their interrelationships in relation to how they measure the overall construct. Lipscomb et al. (2007) noted that the *measurement model* should, in optimal circumstances, be “the operational counterpart to the conceptual model, with the specified domains taking concrete form as constructs to be measured via the items included in the instrument” (p. 146).

Responsiveness refers to the ability of an instrument to detect changes over time, while *sensitivity* refers to the ability of an instrument to highlight differences within a cross-section of individuals (p. 146). In general, the larger number of items within a scale and the more response alternatives associated with each item (i.e. a minimum of five response choices per item), the more responsive to change the instrument is over time (Langenhoff et al., 2001). This need for sensitivity and responsiveness to change must be balanced, however, with practical considerations relative to length and ease of completion within cancer populations. Timing of administration should be consciously scheduled, keeping considerations of the disease and treatment trajectory as well as study design in mind (Langenhoff et al., 2001). Assessing change over time also requires multiple administrations, one prior to treatment and, at minimum, one following treatment at a strategic point (Nayfield, Ganz, Moynour, Cella, & Hailey, 1992).

Interpretability refers to the ease with which meaning can be gleaned from a quantitative score on an instrument (Lipscomb et al., 2007). *Burden* encompasses the work load (i.e., energy, time, etc.) on both the participant and administrator. The *mode of administration* (i.e., self-report, observer ratings, interview, computer-assisted

approaches, performance ratings) may directly impact the degree of burden on both parties. Apart from the validity and reliability considerations that are pertinent to any instrument, the final QOL rating category entails *cultural and language adaptations*, that is their availability as well as their conceptual and linguistic equivalence (Lipscomb et al., 2007). Consideration of the aforementioned evaluation criteria further assist researchers in selecting QOL instruments that optimally fit their research goals or the purposes of the respective clinical trial.

Challenges in Researching QOL

Despite this increased advocacy and appreciation for the utility of QOL information provided by participating survivors, there remain many challenges inherent in accurately measuring QOL. Access to patients in various diagnostic and treatment groups as well as their retention is a recurrent hurdle (Cella & Tulsky, 1993). An impaired health status may contribute to missing or misunderstood items or inconsistent reports. Researcher time is ultimately required to monitor incoming data for completeness and accuracy (Cella & Tulsky, 1993). Additionally, because of the rapid pace of change within treatment delivery, QOL information may concurrently become outdated as new cohorts of individuals receive variations in or altogether novel treatments (Rowland, 1998). As new treatments or alterations to standard chemotherapeutic, radiation or medication dosages are made, QOL impacts will likely alter in tandem, ultimately necessitating new research needs. As this new information is acquired from varying diagnostic and treatment groups, it also remains unclear what constitutes success relative to survivorship outcomes (Rowland, 1998). Specifically, whether these

survivorship outcome markers are determined on a personal, clinician, cohort or national level remains variable. Best methods of translating this acquired psychosocial data from descriptive to applied information that serves to improve patient care, monitoring, and interventions also remains a challenge within and across institutions (Rowland, 1998).

In summary, QOL data yields invaluable information on the multidimensional functioning of a patient, coming from the most knowledgeable source, the patient. This psychosocial information, which is influenced by numerous variables that often are ancillary to treatment variables, may or may not concur with the perceptions of outside observers or objective survivorship markers (e.g. tumor response, hemoglobin level). Regardless of its agreement with other sources of acquired data, QOL data provides some of the best opportunities for entry into the private world of the respective survivor and her or his acceptance of this current level of functioning. It is fortunate, then, that QOL is now included in clinical trials.

Entry of QOL into Clinical Trials

One of the most frequent contexts for QOL assessments is in clinical trials, during which patients often are randomized to treatments and a number of biological and psychosocial variables, including QOL, are examined over the treatment trajectory (McQuellon & Duckworth, 2009). Research by Sugarbaker, Barofsky, Rosenberg, and Gianola (1982) serves as an early example of the entry of psychosocial assessment in a medical setting as well as an illustration of how the acquisition of patient-rated, psychosocial data can, in turn, impact subsequent treatment decision-making on the part of clinicians and patients.

In 1982, Sugarbaker et al. randomized 26 patients with soft tissue sarcoma to one of two groups in a clinical trial: 1) amputation plus chemotherapy or 2) limb-sparing surgery in conjunction with chemotherapy and radiation. Prior to measuring the impact of these respective treatments on the patients' QOL, the researchers hypothesized that those patients whose limbs were spared would report improved QOL over their counterparts who received amputations. Upon receipt of the QOL data, however, the researchers obtained a clearer understanding of the impact of treatment on these individuals' lives and quickly discovered their hypothesis was incorrect. The limb sparing treatment did not lead to enhanced QOL when compared to the amputation treatment. Additionally, the patients who received the limb sparing treatment with corresponding chemotherapy and radiation actually reported significantly reduced sexual functioning when compared to the individuals who received an amputation. The authors speculated that these findings were likely attributable to the greater toxicity to which the limb-spared patients were exposed from the chemotherapy and radiation.

Sugarbaker et al. (1982), whose hypothesis was proven incorrect, ultimately concluded that it is essential to assess QOL impacts post-treatment, as “an improvement in quality of life which seems self-evident may not really exist” (p. 22). Measuring survival in isolation does not assist researchers and patients in making decisions about whether gains in quantifiable time are worth the morbidity and potential QOL impairments (American Society of Clinical Oncology, 1996). Likewise, treatments may offer benefits other than increased survival time including palliation of pain from tumors or blockages, and these benefits may only be noticeable upon the analysis of QOL data

(Cella et al., 1990). Understanding the *actual* psychosocial impact of treatments facilitates informed patient decision making, greater attention to and energy towards patients' psychosocial needs on the part of all medical and mental health parties, as well as improved doctor-patient relations (Sugarbaker et al., 1982). Not surprisingly, since the days of these earlier clinical trials, the inclusion of QOL assessment has continuously become a more standardized component of clinical trial research and of cancer treatment and assessment in general. Numerous governing bodies and associations, including the American Society of Clinical Oncology (1996) and the Food and Drug Administration (Johnson & Temple, 1985), have formally underscored the importance of QOL measurement and implications in the form of standards and practice recommendations.

QOL of Patients Receiving CS+HIPEC

Although the number of investigations entailing candidates and recipients of CS+HIPEC has been limited (Confuorto, Giuliano, Grimaldi, & Viviano, 2007; McQuellon & Duckworth, 2009), the body of literature pertaining to the procedure and the QOL of its recipients continues to grow. Only ten QOL articles involving individuals who received this procedure were located, one of which (McQuellon, Gavazzi, Piso, Swain, & Levine, 2008) is a review of existing literature and recommendations for future practice. It is evident, then, that many gaps remain in this literature base.

In a recent review of these QOL studies, McQuellon and Duckworth (2009) offered many observations and highlighted noticeable trends across studies. While they underscored the potential for successful outcome and subsequent extended life following the CS+HIPEC procedure, their clinical and consultation experience with members of

this population has deepened their respective understandings of the severe complications that may occur post-treatment, significantly impacting QOL. Therefore, while it is the best, and often the only, treatment option for many individuals with peritoneal surface malignancies, CS+HIPEC poses the possibility of both short-term and long-term risks to the candidate's physical and psychological health and overall QOL (McQuellon & Duckworth, 2009).

Typically, those with better performance statuses (i.e., those who are in better overall health) prior to surgery fare better during and post-treatment (Levine, Stewart, Russell, Geisinger, Loggie, & Shen, 2007; McQuellon & Duckworth, 2009), suggesting the importance of stringent selection criteria. A subset of patients will die from complications and morbidities, and those with existing complications or poor performance statuses may face these risks to a greater extent. Similarly, those with more physical symptoms prior to the CS+HIPEC procedure may immediately report improved post-treatment QOL scores, while those with fewer physical symptoms prior to the procedure may comparatively report more significant reductions in QOL in the acute recovery phase (McQuellon et al., 2001). The subsequent post-treatment recovery pattern often varies, therefore, as a consequence of variations in pre-surgical performance status, primary tumor site, and surgical variables, among other things. In general, however, the majority of candidates can anticipate returning to relatively normal functioning by three to six months, with some individuals needing up to 12 months to achieve recovery (McQuellon & Duckworth, 2009). Few individuals return to normal functioning, and therefore achieve their respective baseline QOL, prior to three months, and many report

they experienced a more debilitating post-treatment experience than anticipated (McQuellon & Duckworth, 2009). Finally, between 20-30% of patients can be expected to endorse depressive symptoms when monitored over the 12 months following this surgical and chemotherapeutic procedure (McQuellon & Duckworth, 2009).

In summary, individual differences in both pre- and post-treatment functioning varies to a great extent. Prospective candidates can generally anticipate a decline in physical functioning and general QOL during the acute recovery phase, with subsequent improvements over time. Examining findings from each of the located QOL studies pertaining to this population leads to a clearer understanding of the spectrum of experiences as well as the general trends.

Acute QOL. The first QOL study located of individuals following CS+HIPEC was published in 2001 (McQuellon et al., 2001). In this study, all patients consecutively treated at Wake Forest University Baptist Medical Center (WFUBMC) between September 1, 1995 and December 31, 1997 were eligible. A total of 64 patients consented and were interviewed prior to CS+HIPEC; 48 patients were interviewed post-operatively (mean=13.2 days post-procedure); and 41, 39, and 31 patients were assessed at three, six, and 12 months, respectively. A total of 23 patients completed the assessment battery at all five collection points.

For this collective group, mean QOL scores on the Functional Assessment of Cancer Therapy-Colon (FACT-C) dropped significantly from the baseline to post-procedure measurement, rebounded to levels that were better than baseline by three months, and subsequently showed improvement over the course of the year (i.e. six and

12 month time points). A statistically significant overall effect was noted on physical well-being ($p = 0.0025$), emotional well-being ($p = 0.0001$), functional well-being ($p = 0.0044$), colon subscale ($p = 0.0229$) and overall QOL scores ($p = 0.0076$). The subgroup of patients with malignant ascites (i.e. the accumulation of fluid that contains cancer cells within the abdominal area; National Cancer Institute, n.d.), however, demonstrated the opposite trend, presenting with lower baseline QOL component scores and improved post-procedure QOL scores. These findings within this subgroup likely reflect the literal removal of the cumbersome ascites, resulting in immediately apparent reduced physical symptoms and discomfort. McQuellon et al. (2001) noted that functional status impairment reports resembled the collective QOL trend, with impairments increasing significantly from baseline to post-procedure and then demonstrating continued improvement throughout the year.

Similar to McQuellon et al. (2001), other researchers reported that the physical health of these patients decreases for the acute time period following surgery and then demonstrates improvement with time. At the 57th Annual Cancer Symposium, Alexander et al. (2004) reported QOL findings from 73 patients with peritoneal surface malignancies who underwent debulking and peritonectomy, major organ resection, followed by continuous hyperthermic chemotherapy perfusion between February of 2000 and July of 2003. Specifically, they examined patients' generic QOL, as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (Ware & Sherbourne, 1992), and condition-specific QOL, as measured by the FACT-C, at baseline, six weeks, three, six, and nine months post-procedure. Resembling the trend

reported by McQuellon et al. (2001), Alexander et al. (2004) found that the physical component scores of the SF-36 decreased significantly from baseline to six weeks ($p < 0.0001$), yet did not differ significantly from baseline scores at three, six, and nine months.

Targeting 35 patients consecutively treated with CS+HIPEC from 2001-2005 in a phase II study at the University of Minnesota, Tuttle, Zhang, Greeno, and Knutsen (2006) also examined longitudinal QOL scores. QOL scores were measured at baseline, four, eight, and 12 months. The overall FACT-G ($p = 0.0351$) and FACT-C ($p = 0.0371$) scores as well as the emotional well being ($p = 0.0026$) and functional well being ($p = 0.0030$) subscale scores demonstrated significant increases across time. Specifically, the baseline and four month scores were not significantly different, yet scores increased to surpass those of baseline at eight and 12 months. Given that Tuttle et al. (2006) did not assess QOL post-procedure until four months, it remains unknown if the established trend (i.e. a decrease in physical well-being during the acute recovery phase (McQuellon et al., 2001; Alexander et al., 2004)) actually occurred. It is likely that these patients experienced decreased physical and functional well-being during the first few months of recovery yet reported physical well-being levels that resembled their baseline levels by four months. These findings suggest the importance of strategic timing of assessments post-CS+HIPEC. Ultimately, Tuttle et al. (2006) concluded that those who live to be survivors often report improved and acceptable QOL because of the reduction of physical symptoms.

Finally, McQuellon (2007) published additional findings detailing post-CS+HIPEC health outcomes. A total of 96 individuals completed their baseline instrument, while 38, 32, and 24 individuals completed the three, six, and 12 month instruments respectively. During the study, 31 participants died and 20 participants withdrew from the study or reported being too sick to complete the packet.

With the exception of the social/family well-being subscale, all FACT QOL subscale scores as well as the overall QOL score demonstrated significant changes over time (McQuellon et al., 2007). Those who remained in the sample across time demonstrated improvements in overall mean FACT scores from baseline to 12 months. For the 38 participants who completed the three month survey, all subscale QOL scores, with the exception of the physical well being subscale scores, had returned to or exceeded baseline levels. Again, these findings are consistent with those of previous researchers (Alexander et al., 2004; McQuellon et al., 2001). An examination of the corresponding SF-36 subscales further explains these findings, with the physical functioning, role functioning, and bodily pain subscales demonstrating a significant overall increase from baseline to 12 months. Specifically, and in line with previous findings, the three aforementioned scales decreased significantly from baseline to three months and then exceeded baseline levels to achieve their highest scores by six months. From these findings, one can ascertain that a significant percentage of patients continue to report physical limitations at the three month period, after which these symptoms begin to dissipate. It is important to note, however, that all of the SF-36 scale scores, with the exception of the vitality subscale, remained below the general population norms, meaning

this collective group continued to experience less than optimal health relative to the general population (McQuellon et al., 2007).

In summary, the findings of the aforementioned researchers reflect the fluctuations in QOL over time, primarily as a function of physical well being and functional status. Specifically, with the exception of the subgroup of patients with malignant ascites (McQuellon et al., 2001), the patients described by these researchers demonstrated significant decreases in QOL and functional status from baseline to the first few months post-CS+HIPEC (Alexander et al., 2004; McQuellon et al., 2001; McQuellon et al., 2007). While the physical and functional well being of some patients continue to improve over the next nine months (Tuttle et al., 2006), the physical and functional status of others typically returns to baseline levels (Alexander et al., 2004). Although these scores demonstrate movement over time, McQuellon et al. (2007) noted that the majority of the scores still range below those of the general population.

Trends in mental health also can be extracted from this longitudinal data. McQuellon et al. (2007) noted that the emotional well-being subscale scores of participants were generally the same or higher than baseline levels by three months. Regarding depressive symptoms, McQuellon et al. (2001) noted a progressive decrease in the percentage of patients endorsing clinically significant depressive symptoms across the first four time points, up until the 12-month assessment period. One year post-procedure, the percentage of participants expressing depressive symptoms increased relative to the six-month assessment period yet still remained lower than the percentage of individuals expressing depressive symptoms at baseline (i.e. baseline (38%), post-procedure (33%),

three months (23%), six months (21%) and 12 months (29%)). Although these depression scores are likely inflated by some of the significant physical symptoms experienced by members of this population, the unusually high percentages reflect the patients' continued struggles and the potential need for psychosocial interventions. In a similar trend, Alexander et al. (2004) found that the mental component scores of the SF-36 increased significantly from baseline at six weeks ($p = 0.006$) and three months ($p = 0.014$) (indicating fewer depressive symptoms) yet did not differ significantly from baseline at six and nine months. Tuttle et al. (2006) reported that the emotional and functional well being scores of their participants were significantly improved at eight and 12 months relative to baseline, suggesting long-term improvement in the occurrence of depressive symptoms. Interestingly Tuttle et al. (2006) also noted that the occurrence of an adverse event (such as an intra-abdominal abscess) correlated significantly with smaller increases in QOL scores.

Overall, these findings related to the mental health of patients in the acute recovery period post-CS+HIPEC reveal immediate reductions (relative to baseline) in the percentage of patients experiencing depressive symptoms (McQuellon et al., 2001) and improvement in general emotional well-being in assessments following surgery (Alexander et al., 2004). All researchers noted at least some positive movement in these mental health scores over time (McQuellon et al., 2001; Alexander et al., 2004; Tuttle et al., 2006), with some noting significant positive differences between baseline and endpoint assessments (Tuttle et al., 2006) and others noting a leveling off, with no long-term differences (Alexander et al., 2004).

Long-term QOL. Researchers also have considered how long-term survivorship issues differ from those that are acute in nature. McQuellon et al. (2003) examined a cohort of individuals not targeted in their initial study, those living three or more years post-CS+HIPEC. In conducting this descriptive study, the researchers were particularly interested in the kind and degree of persisting deficits, that is, in the overall price of extended survival for the individuals who experienced peritoneal metastases. Considering no long-term QOL data was available for reference for this population, McQuellon et al. (2003) targeted overall QOL scores, psychosocial concerns and depressive symptoms in those living three or more years post-procedure. All patients receiving this procedure at WFUBMC, treated consecutively between January 1, 1992-December 31, 1997 and demonstrating no evidence of disease were eligible for the study. At the time of the study, 109 individuals had been treated at WFUBMC. Of those, only 29 had survived for three or more years and 12 did not want to participate. Data from a total of 17 participants (mean time since procedure= 5.3 +/- 1.6 years) were therefore gathered. For ten of the participants, data were compared to existing baseline QOL scores.

At the time of the study, McQuellon et al. (2003) found that long-term functional well being ($p = 0.01$), physical well being ($p = 0.05$) and overall QOL scores ($p = 0.02$) were improved relative to baseline scores for those participants with available data and did not differ significantly from three, six, and 12 month QOL scores. Likewise, mean scores on a general QOL measure, the SF-36, were 68.2+/-11.5 for the long-term survivors, compared to 67.0 +/-23.4 for the general population (McQuellon et al., 2003).

These findings suggest that the acute deficits that are present immediately following treatment dissipate with time, and the achievement of a life of quality that is comparable to that of the general population is possible for those who survive and recover from the procedure. McQuellon et al. (2003) reported that no one who survived three or more years regretted having the procedure. Alternate concerns experienced within the 30-day time frame of the study for greater than 15% of participants included concerns related to sleep quality, sex life, and fears of recurrence. Only one individual endorsed sufficient depressive symptoms to be considered a probable “case” (McQuellon et al., 2003). Overall, these long-term survivors achieved a quality of life that resembled their general population peers.

Using the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Cancer 30 (EORTC QLQ-C30), Schmidt, Dahlke, Klempnauer, Schlitt, and Piso (2005) also attempted to assess the QOL of 67 survivors of peritoneal surface malignancies from 11 different sites treated between March 1995 and February 2003. The overall morbidity rate in this population was 34%; the post-operative mortality rate was 4.5%, the median stay in the intensive care unit was 5 days (range 1-116), and the median hospital stay was 25 days (range six-116). At the time of the study (mean time post-procedure=4 years), 25 individuals were still living. Of those individuals, 20 returned the surveys, the largest concentration of which included individuals with a primary diagnosis of appendix carcinoma. The mean QOL score (62.6) was measurably lower than that of the general Norwegian population (73.3). Patients who received a stoma (i.e. an opening from the inside to the outside of the body

created via surgery; National Cancer Institute, n.d.) during the procedure (n= two) reported significantly lower QOL estimates (mean= 16.7) than their CS+HIPEC peers. The most disabling symptoms reported by this group included pain, followed by insomnia, followed by fatigue. The authors underscored the importance of carefully selecting surgical candidates and the potential existence of a better prognosis for individuals with peritoneal surface malignancies from specific origins (i.e. appendix carcinoma). If carefully selected, the potential for extended life expectancy and the achievement of an acceptable QOL is attainable (Schmidt et al., 2005).

The QOL of subgroups. Sub-groups of patients who received CS+HIPEC also have been examined. For example, Jess et al. (2008) focused on a specific group of patients who received CS+HIPEC, individuals with pseudomyxoma peritonei (PMP) (i.e. peritoneal implantation metastases originating from cells that escape following a surgical removal or the rupture of ovarian cystadenoma, resulting in abdominal wall and intestinal papilla and an abdominal cavity filled with mucus-like fluid; Thomas, 1997). Specifically, their participants consisted of 23 patients who underwent this procedure at Aarhus University Hospital in Denmark. Patients completed QOL questionnaires at clinic visits prior to the procedure and at three, six, 12, 18, and 24 months post-procedure. The relative symptom weakness for individuals with this specific diagnosis, PMP, is apparent, as baseline scores of patients were comparable to population norms. The median hospital stay for this cohort was 18 days, although four patients were transferred to an alternate hospital stay for subsequent stays. No one died within 30 days post-procedure. Leading morbidities post-procedure included fever of unknown etiology,

urinary tract infection, intraabdominal abscess, fistula to the Hartmann' stump, and fistula to the vagina. All morbidities improved following treatment. Similar to previous studies, statistically significant decreases in the role physical subscale and physical dimension summary scale score from baseline to three months were observed. Scores returned to preoperative levels by six months, and no significant differences were noted relative to baseline scores in subsequent measurements. Jess et al. (2008) concluded that, despite the extensiveness of the procedure and the high rate of morbidity, the QOL impact of this procedure on individuals with PMP is relatively minor and only transitory.

Although beyond the scope of this dissertation, numerous other researchers have reported their results of CS+HIPEC with various sub-populations, including those with malignant ascites (Garofalo, Valle, Garcia, & Sugarbaker, 2006), appendiceal neoplasms (Stewart et al., 2006; Sugarbaker et al., 2006), malignant peritoneal mesothelioma (Feldman et al., 2003; Yan, Edwards, Alderman, Marquardt, & Sugarbaker, 2007), sarcomatosis (Lim et al., 2007), and dissemination from the colon/rectum (Verwaal et al., 2003).

Case study. Finally, McQuellon and Duckworth (2009) attempted to highlight the QOL impact of this specific surgical oncology procedure by means of an alternate methodology, a case study. Specifically, these researchers and clinicians wanted to offer a descriptive picture of the QOL impacts on one survivor and additionally illustrate how QOL data collection and monitoring can be used to enhance clinical care. McQuellon and Duckworth (2009) described the case of a 50-year-old, married female whose symptoms preceded her actual diagnosis of mesothelioma with peritoneal metastases by

several months. Her baseline FACT score, acquired prior to CS+HIPEC, of 49 reflects an array of symptoms and significantly impaired QOL. Likewise, she reported significant depressive symptoms on the CES-D, therefore warranting a pre-surgical phone call. The patient described experiencing numerous physical symptoms and fatigue, which prevented her from working. She also described ruminating about her condition worsening. No further psychological care was recommended at that time.

The patient proceeded to enter the hospital for CS+HIPEC. In addition to the debulking and peritonectomy, she had multiple organs resected. She was hospitalized for numerous months in her regional hospital as a consequence of nausea, inadequate nutrition and substantial weight loss. Again, the acquisition of QOL questionnaires at three months that revealed impairments in QOL (score of 58) due to physical and functional deficits, trouble meeting the needs of her family, fears of recurrence, as well as depressive symptoms warranted a follow-up phone call. At a post-procedure surgical consult, the physician recommended a consultation with a mental health professional. In a mental health consultation, the patient noted she was improving physically and emotionally, so no further counseling was arranged at that time.

At six months, the patient again returned the QOL questionnaires with a FACT score of 62. Despite the continual improvement over time (i.e. 49, 58, 62), this most recent score continued to reflect significant QOL impairments, including many chronic impairments and frustration over her QOL. At a nine month surgical consult, the physician was troubled by her flat affect and lack of excitement when he revealed that she was doing extremely well. From a medical standpoint, she was doing very well; from

a psychosocial standpoint she was not. She was exhibiting some mild depressive symptoms, had only attained roughly 50% of her normal energy levels, suffered from many chronic problems, and was unable to return to work. She was not pleased with the quality of her life and was frustrated when she was told everything looked good from a medical standpoint based on a lack of residual disease. She resumed meeting with the mental health professional for counseling and survivorship care planning that entailed strategies for meeting her biopsychosocial needs.

This case illustrates the complexities of the recovery trajectory for many individuals following CS+HIPEC. Her QOL scores, as measured by the FACT, continued to improve significantly over time (49, 58, and 62), yet the post-procedure complications, the slow recovery process, the lingering physical symptoms and the overall impact on the quality of her life displease her. Although no residual disease was present, she continued to face many challenges. A biopsychosocial approach considers the multidimensional impact of such a procedure, ensuring all patient needs and concerns are considered and addressed. From this, it seems clear that focusing exclusively on the medical results of such a traumatic and impactful procedure is insufficient.

Based on this review of the results of all CS+HIPEC QOL studies located within the literature, some observations can be made. First, CS+HIPEC patients have been insufficiently studied. Much remains to be investigated. Of the results that are available, one can conclude that patients experience decreases in QOL during the acute recovery phase (i.e. the first months post-procedure) due to impairments in physical and functional status. QOL scores typically approach baseline levels by three to six months, and many

experience prolonged life expectancies that would not have possible without this procedure. On the other hand, many experience significant morbidities and are likely not represented in existing studies. Datasets likely capture the optimal cases, excluding many cases full of extreme suffering. Reducing the sample size down to a single case study, McQuellon and Duckworth (2009) captured some of the intricacies and unexpected hurdles of the recovery process and the frequent incongruence relative to achievement of a medical recovery and the achievement of a desired quality of life. Additionally, this case illustrated the importance of attending to the biological, psychological and social needs of every patient. QOL assessment and its respective clinical application is one way of accomplishing this task in a medical environment. One limitation, however, is that QOL researchers often insufficiently investigate the construct of sleep quality.

Sleep Quality

Throughout history, cultures of the world have offered unique, often mystical, interpretations of both the precipitating causes and subsequent meanings of sleeping and dreaming. The ancient Greek culture gave us Nyx, the primordial goddess of night, who burrows in the Underworld by day and predictably emerges at dusk to unfold night across the earth's sky (Naiman, 2006). Inevitably following behind in her ephemeral dusk is her son, Hypnos, inducing sleeping and dreaming in those below. In addition to this picturesque offering provided by the Greeks, sleep has been creatively conceptualized as a time for the soul to occupy an alternate world; the result of blood-filled vessels forcing the brain into an alternate state; the brain's response to vapors released following digestion; even the result of the brain's exposure to a large amount of "hypnotoxins"

(Moorcroft, 2003, p. 15). In the middle of the 20th century, however, alongside technological advances in sleep measurement methods, many of these notions faded away, like the evanescent dusk.

The development and utilization of polysomnography prompted changes in the comprehension of the process and implications of sleep, ultimately leading to a valid understanding of the intricacies of both sleep and wakefulness (Moorcroft, 2003).

Polysomnography entails the measuring and recording of electrical energy released from bodily organs. Recordings from brain waves (electroencephalogram, EEG), neck muscle tension (electromyogram, EMG), and eye movements (electrooculogram, EOG) have solidified our understanding of the respective stages of sleep and the fairly predictable pattern of sleep stage cycling (Moorcroft, 2003). The stages (alert wakefulness, drowsy wakefulness, sleep stages one, two, three, four and rapid eye movement (REM) sleep) are differentiated by unique features in polysomnographic readings and are more accurately conceptualized as qualitatively different, rather than progressively deeper (Moorcroft, 2003). Stages one, two, three and four are collectively known as non-REMs (NREM) sleep, while stages three and four also are referred to as slow wave sleep (SWS) (Moorcroft, 2003).

Defined as “a reversible behavioral state of low attention to the environment typically accompanied by a relaxed posture and minimal movement” (Moorcroft, 2003, p. 24), sleep is an essential, rejuvenating component of all human existence of which we have gradually become more informed. Certain areas of the brain (working in an integrated fashion), along with neurotransmitters and various substances found in the

cerebrospinal fluid and blood, have influential roles in both wakefulness and sleep (Moorcroft, 2003). Rather than a simple and passive process, then, sleep is the product of active processes within the brain (Moorcroft, 2003).

Of interest to researchers is often the reported quality of this sleep. Defined as the “quantitative aspects of sleep, such as sleep duration, sleep latency, or number of arousals, as well as the more purely subjective aspects, such as ‘depth’ or ‘restfulness’ of sleep” (p. 194), Buysse et al. (1989) stated that this construct and its respective measurement are important for numerous reasons. First, complaints and concerns related to sleep quality are common in the population, suggesting large numbers of individuals in need of intervention. Secondly, these sleep-related concerns may, in fact, be symptoms of actual medical or sleep disorders, therefore warranting attention (Buysse et al., 1989). Buysse et al. (1989) underscored the continued disagreement within the field relative to the specific components that define sleep quality and their relative importance. Often, the needs of the population under examination and the research goals of the respective study may define which aspects of sleep quality are most salient for a respective investigation (Buysse et al., 1989). With that stated, however, the multidimensional nature of sleep quality cannot be understated. Assessing overall sleep quality by means of one question or one component is insufficient.

Although QOL is a construct that is multidimensional in nature, many additional constructs of importance are not routinely included in general QOL assessments. If these constructs are of interest to the researcher or are of significance to the survivorship of a particular diagnostic or treatment group, additional assessment of those respective

constructs may be necessary. Sleep quality is one such example that may warrant supplemental investigation in some populations, including survivors who have had CS+HIPEC. McQuellon et al. (2003) and Schmidt et al. (2005) reported that sleep quality and insomnia, respectively, are commonplace concerns among survivors of CS+HIPEC. These findings suggest the need for further investigation of and attention to the sleep quality of CS+HIPEC survivors by means of multidimensional assessments designed specifically for the assessment of this construct.

Buysse et al. (1989) included the following seven components in their assessment of sleep quality: sleep latency (i.e., the time it takes to fall asleep; Moorcroft, 2003), sleep duration, habitual sleep efficiency (i.e., the proportion of that respective sleep period actually spent asleep, rather than awake; Moorcroft, 2003), sleep disturbances, use of sleeping medications, daytime dysfunction, and subjective sleep quality. The aforementioned components of sleep quality utilized by Buysse et al. (1989) in their research are likewise those areas that are routinely assessed in the clinical interviews of patients who present with sleep-related disturbances. Despite our advanced understanding of this construct, the development of tools that sufficiently measure its quality, and the prevalence and potential severity of sleep disturbance and impaired sleep quality, many cite the overall paucity of studies in which investigators have examined the multi-component nature of sleep quality and argue that we have made insufficient progress in measuring and attending to certain sub-populations' sleep-related concerns over the years.

Prior to researching sleep quality, one must acquire at least a basic understanding of the sleep process and the plethora of factors potentially influencing this process. The brief overview of some of the factors influencing the sleeping and waking states that follows will permit the reader to acquire a crude understanding of the bodily processes during sleep.

The Body During Sleep

To remain awake and responsive to stimuli, a person needs activation in the cerebral cortex and forebrain (Moorcroft, 2003). The ascending reticular activating system (ARAS; a portion of the reticular formation) receives information transmitted from the forebrain and alternate sensory systems and, in turn, utilizes neurotransmitters (e.g. acetylcholine, norepinephrine, glutamate) to activate the cerebral cortex in various ways (Moorcroft, 2003). Other portions of the brain, including the raphe (located in the middle of the brainstem) and the locus coeruleus (on top of the pons) also utilize neurotransmitters to activate the forebrain, thus promoting wakefulness. Additionally, within the suprachiasmatic nucleus (SCN), the circadian clock serves to regulate an individual's bodily rhythm and subjective sense of day and night (Moorcroft, 2003; Schenck, 2008). Although influenced by zeitgebers (or time givers), such as light, the cells within the SCN work together to create this individualized bodily rhythm and to impact additional hormonal and physiological activities within the body (Moorcroft, 2003). This rhythm enables us to have an "internal biological (subjective) day and night that usually enables us to mirror and prepare for the forthcoming change between external (objective) day and night" (p. 48).

As subjective night begins approaching, a person does not simply fall into sleep instantaneously. Rather, gradual and successive changes occur, and a person may transition in and out of sleep numerous times prior to maintaining sleep (Moorcroft, 2003). Throughout wakefulness, a byproduct (i.e., adenosine) of certain molecules progressively builds up in the system, contributing strongly to the intensity of sleepiness while waking and subsequently impacting the amount of time spent in certain sleep stages while sleeping (Moorcroft, 2003). Additionally, the basal forebrain, thalamus and anterior hypothalamus, along with other areas of the brainstem and forebrain, utilize neurotransmitters to reduce activity in parts of the brain when sleep onset arrives. Other factors that concurrently serve to impact sleepiness include prior amounts of sleep, the point in the circadian phase, the amount of time spent waking, age, health status, context, and recent drug use (Moorcroft, 2003).

As a person begins transitioning into stage I sleep, certain polysomnographic signs are notable. For instance, EOG readings of slow eye movements, along with EEG readings of alpha waves (i.e. moderate intensity, intermediate frequency brain waves that occur in persons who are awake yet drowsy) and then theta waves (i.e., moderate to low intensity, intermediate frequency brain waves occurring in sleeping individuals) indicate entry into this initial sleep stage (Moorcroft, 2003). The presence of K-complexes (i.e., waves lasting approximately $\frac{1}{2}$ second, exhibited on polysomnography as large peaks followed by small valleys) or spindles (i.e., moderately fast and intense oscillations lasting approximately $\frac{1}{2}$ to $1\frac{1}{2}$ seconds) on EEG readings, along with the absence of eye movements indicates a movement into stage II sleep. Once the large and slow delta

waves (i.e., brain waves that are intense and of low frequency) are noted in the EEG, stage III sleep, or the beginning of SWS, has commenced. After approximately 30 minutes of SWS, an individual typically will drift back into stage II sleep, exhibiting the characteristic stage II K-complexes, spindles, and theta waves for 20 minutes or so, and then re-enter SWS (Moorcroft, 2003; Schenck, 2008).

As an individual enters this NREM sleep (i.e. stages I-IV sleep), neurons are operating at a lower activity and metabolic rate relative to waking levels (Moorcroft, 2003). Brain feedback systems continue to interact and maintain bodily stability, yet at a lower level as well. These effects are partially a consequence of the actions of certain parts of the brain (e.g., basal forebrain and thalamus) using inhibitory neurotransmitters and neuromodulators to reduce forebrain activity (Moorcroft, 2003). The parasympathetic nervous system (PNS) is predominant during NREM sleep, maintaining the body's resources and conserving energy in a restful manner (Moorcroft, 2003). The heart rate is slower and blood pressure is lower. With the exception of those areas responsible for NREM sleep, most brain areas are receiving less blood flow than during the waking state (Moorcroft, 2003). Rather than behaviorally controlled, breathing is automatic and serves to regulate oxygen and carbon dioxide levels in the blood, albeit at levels that deviate somewhat from the waking state (i.e., less oxygen and more carbon dioxide in the blood). Less air is leaving and entering the lungs each minute, and airflow resistance increases. Breathing, therefore, requires extra effort relative to waking, yet is deeper overall (Moorcroft, 2003). The body temperature drops during sleep onset, with the body temperature reaching its nadir approximately six hours following sleep onset.

The body continues to regulate its temperature by means of blood flow in the same manner as during the waking period. Overall, the NREM state might best be described as restorative and calm, with systems continuing to function but on a lower and slower level (Moorcroft, 2003).

Approximately 80 minutes following sleep onset, however, signs of the first REM sleep appear, and the aforementioned patterns and system functioning changes. Specifically, during REM sleep, (i.e., the stage during which dreaming predominantly occurs), EEG readings denote sawtooth-appearing brain waves (i.e. mixed frequency, low intensity waves having a notched appearance); EOG readings demonstrate bursts of eye movements; and EMG readings denote a low degree of muscle contraction and tension (Moorcroft, 2003). Both tonic (i.e., constant) and phasic (i.e., short-lived) aspects of REM sleep can be noted. As opposed to the slower, yet regular, functioning of the bodily systems in NREMS, irregularity characterizes REM sleep (Moorcroft, 2003; Schenck 2008).

Certain parts of the brain, including the back of the pons, midbrain, thalamus, temporal and occipital cortical lobes, and parts of the limbic system, are activated to a greater extent in REMS than during waking states, and specific neuronal activity patterns occur that do not otherwise occur in waking (Moorcroft, 2003). The pons is the section of the brain that is essential for REMS. Specifically, the REM-on cells within the pons interact with midbrain, medulla, and hypothalamus cells by means of specific neurotransmitters (i.e., acetylcholine, GABA, glycine, and glutamate) to produce both the tonic and phasic aspects of REM sleep. An example of one of the primary tonic aspects

of REMS is muscle paralysis. Although motor impulses from the forebrain continue, actual muscle movements are blocked by means of glycine originating from neurons in the medulla (Moorcroft, 2003). This temporary muscle paralysis prevents individuals from acting on or responding to their vivid, seemingly real dreams. In a similar manner, lower sections of the brain (i.e., the brainstem) override local reflexes that are operating the bodily systems, ultimately not taking into account or acting on the sensory information received from these systems throughout this stage (Moorcroft, 2003).

This irregularity and lack of responsiveness to sensory stimuli is underscored further with an examination of the functioning of many of the major organ systems during the REM sleep. Many central nervous system neurons are more metabolically active in the tonic phase of REM sleep than during waking, highlighting the large amount of mental activity that is truly occurring during this time. Blood flow increases substantially in some portions of the brain (especially during phasic stages), with some areas receiving 50-200% more blood flow than during waking. Similar to NREM sleep, the PNS is dominant during tonic aspects of REM sleep. The PNS remains active into the phasic stages of REM as well, yet the sympathetic nervous system (SNS) (i.e. the “fight or flight” response that dominates during threats to bodily integrity) sporadically activates certain organ systems in an intense manner as well (Moorcroft, 2003). During the phasic components, neurons exhibit bursts of sporadic activity in certain brain areas, including the visual areas (Moorcroft, 2003). Heart rate and blood pressure during tonic REMS are slow and low, respectively, and are much less responsive to the blood flow demands of the various organs (Moorcroft, 2003). In phasic REMS, both the heart rate

and blood pressure are highly variable, with increases and pauses. In general, an individual's blood pressure is much higher during phasic REMS, sometimes 30% higher than baseline (Moorcroft, 2003). Breathing in REMS is fast, variable, and irregular (Moorcroft, 2003). Input and output levels of oxygen and carbon dioxide are largely disregarded, and breathing is predominantly behavioral (rather than automatic). Finally, rather than making slight adjustments to regulate the internal body temperature during REMS, the body simply adjusts to its surrounding context. The temperature of the brain increases due to the higher levels of brain activity (Moorcroft, 2003).

In summary, the majority of the bodily systems are not strictly regulated during REM sleep, and there is a general disregard of or reaction to feedback relative to bodily fluctuations (Moorcroft, 2003). Unlike the previous sleep stages, REM sleep is not restful and restorative, nor are bodily systems operating in a routine fashion. Rather, variability and irregularity are the temporary norm. As a consequence, some argue that the body's welfare is somewhat jeopardized during this sleep phase (Moorcroft, 2003). Aside from rest and restoration, however, some of the many hypothesized benefits gained from this unique sleep stage include memory consolidation, the stimulation and maintenance of synaptic connections, and emotional regulation following the processing of dream content (Moorcroft, 2003).

Throughout the night, the sleep stages will continue to cycle in a lawful pattern, yet the time allocations for each vary. For instance, more SWS occurs in the beginning of the night relative to REM sleep (Moorcroft, 2003). As the sleep period extends, the REM periods increase progressively, from approximately one to two minutes early in the

sleep cycle to about 30 minutes towards the end of the night. Cutting sleep periods short will, then, reduce the amount of REM sleep (Moorcroft, 2003). Reducing sleep periods significantly and habitually may also result in other adverse effects on the body and performance, highlighting the strong relationship between sleep and health.

Effects of sleep on the body. Naiman (2006) argued that deep sleep attainment is one of the most important investments in our strivings toward optimal health. Much of our knowledge relative to the essential functions of sleep comes from investigations in which sleep has been restricted or altogether deprived in subjects. The effects of such deprivation include impacts on immune functioning, metabolism, psychological states, and central nervous system regulation (Weinhouse & Schwab, 2006), thereby underscoring the multidimensional impact and importance of sleep.

Although some evidence exists that contradicts the notion that rest and restoration are *primary* functions of sleep, one of the longstanding notions is that sleep is “a time of quiescence when the body appears to be able to generally reverse the wear and tear accumulated when awake” (Moorcroft, 2003, p. 268). A certain amount of continuous sleep containing both SWS and REM sleep must occur, however, in order to acquire these proposed beneficial effects (Moorcroft, 2003). This concept that sleep has a restorative function is supported by level of hormone release. Many hormones, including human growth hormone (GH) and the anabolic hormones prolactin, leutenizing hormone, and testosterone, reach their highest levels during sleep (Moorcroft, 2003). GH, released largely in SWS, plays a key role in many biological processes, including immune system functioning, the cellular absorption of nutrients, as well as healthy weight and lean

muscle mass maintenance (Naiman, 2006). Melatonin, which also reaches its peak during sleep, enhances immunity and offers antiviral and anti-cancerous protection as well (Naiman, 2006). The reduced activity levels, energy use and body temperature experienced during sleep also contribute to the restorative effect of sleep on the body (Moorcroft, 2003).

Sufficient amounts of sleep may be necessary for the maintenance of mental health as well. In their research with rodents, Novati et al. (2008) found that chronic sleep deprivation may contribute to the development of symptomology that is characteristic of psychiatric disorders, including depressive symptoms. Specifically, Novati et al. (2008) employed an animal model of sleep restriction and investigated the subsequent impacts on the neuroendocrine and neurobiological systems believed to have a contributory role in the development of depressive systems (i.e., the serotonergic system and the hypothalamic-pituitary-adrenal (HPA) axis). Blood samples were drawn from the rodents who were permitted only four hours of sleep per nycthemeron, and special attention was paid to the adrenocorticotropin (ACTH) and corticosterone responses (Novati et al., 2008). The researchers found no significant impact on HPA axis stress reactivity after one day of sleep deprivation. Following a week of chronic deprivation, however, Novati et al. (2008) noted a diminished pituitary ACTH response in a fear paradigm, potentially due to lowered sensitivity of serotonin-1A receptors and corticotropin-releasing hormone receptors. Novati et al. (2008) concluded that habitual sleep deprivation may precipitate alterations in neurotransmitter receptor systems and neuroendocrine reactivity, as seen in individuals exhibiting depressive symptoms. In

summary, although commonly conceptualized as a symptom of a psychiatric disorder, disrupted or habitually diminished sleep also may serve as a precipitating factor in the development of subsequent problems (Novati et al., 2008).

In addition to recuperation and the maintenance of mental health, numerous other major functions of sleep have been proposed. Researchers have offered evidence suggestive of specific benefits to the brain and local cells, memory consolidation, and even emotional benefits afforded by the act of dreaming (Moorcroft, 2003). The exploration of each of the aforementioned benefits as it applies to the general population is beyond the scope of this dissertation. It is important to realize their relationship to sleep and the fact that certain populations may experience fewer of these benefits, as their sleep periods are more frequently interrupted and their sleep quality is reduced.

Effects of the body on sleep. While sleep impacts human functioning, many aspects of human functioning, whether endogenous, self-induced, or contextual, also have the ability to impact sleep quality. That is, the relationship between the body and sleep is mutually influential. The list of potential variables impacting sleep is extensive, yet a few that are particularly salient to cancer populations include age, stress, pain, medication intake and health status.

Age is an example of an endogenous variable that has relevant implications for sleep. From newborns and small children, to teenagers, to young adults, to middle-aged and elderly adults, noteworthy sleep changes are typical with age (Moorcroft, 2003). Although individual variation abounds relative to these changes, many individuals who are diagnosed with cancer in middle- to late-age already may have noticed changes in

their sleep irrespective of their cancer diagnoses. Common age-related sleep changes experienced by those in later stages of life include difficulty with sleep onset and both longer and more common nighttime awakenings (Moorcroft, 2003). Sleep tends to be lighter and more parceled. Likewise, sleep disorders and many illnesses become more common with age, increasing the likelihood of interrupted sleep due to the disorder itself or the prescribed medication (Moorcroft, 2003). Circadian rhythms tend to phase advance as well, with the desire to sleep and rise both coming earlier (Moorcroft, 2003). The sum of total nighttime sleeping hours is typically reduced to six or seven hours, although the inclusion of daytime naps might make sleeping more evenly spaced throughout the nycthemeron and leave the total sum of sleeping hours in a given time period the same (Moorcroft, 2003). Finally, the examination of polysomnography readings reveals a reduction in SWS, a reduced intensity of delta waves, and a reduction in the total number of REMS in a sleep period (although the same amount of total REM time) (Moorcroft, 2003). Age range alone, then, irrespective of health status, is associated with significant changes in sleep across the lifetime.

Stress and recurrent nightmares also have the potential to impair sleep. Whether transitory or chronic, stress is disruptive to sleep, causing sleep fragmentation and altered amounts of time spent in the various sleep stages (Moorcroft, 2003). Racing thoughts characteristic of anxiety may prevent or greatly postpone sleep until the underlying issues are worked through or dissipate on their own (Naiman, 2006). The increase in numerous stress-related hormones, including adrenal cortical tropic hormone and cortisol, as well as the negative impacts of stress on the immune system can lead to further sleep

fragmentation. Additionally, high levels of stress and troubling experiences often prove inescapable during sleeping hours, symbolically presenting themselves, either thematically or in full, in recurrent dreams (Moorcroft, 2003). Following traumatic situations, individuals may continue to re-experience their respective trauma in nightmares that are even more invasive or panic-inducing than more banal nightmares (Moorcroft, 2003). Associated with such dreams or nightmares are augmented levels of stress, anxiety or depression, traumatic nighttime awakenings, and even phobias related to sleep (Moorcroft, 2003).

Individuals experiencing pain or taking non sleep-related medications also may experience impaired sleep. In a cyclical fashion, sleep affects one's subjective experience of pain, while pain, in turn, impacts sleep quality (Moorcroft, 2003). Specifically, high levels of pain may make sleep disruption and impairment more probable, while reductions in sleep are associated with higher subjective ratings of pain. Similarly, bodily inflammation, a common condition in many diseases and disorders (e.g., digestive reflux, breathing and limb disorders), frequently prevents the host's body from cooling and resting sufficiently to sustain deep sleep (Naiman, 2006). Individuals who are in pain also commonly find themselves in a hospital environment where they encounter nightly disturbances, noises and bright lights that serve to further impair sleep quality (Moorcroft, 2003).

Further, prescription medications taken for non-sleep related conditions, including pain, often impact the brain in ways that effect the sleeping and waking cycle as well (Moorcroft, 2003). Common culprits that impact the sleep/wake cycle include

medications frequently prescribed for depression, anxiety, cardiovascular concerns, breathing disorders, schizophrenia, allergies (i.e. antihistamines), pain relief and nasal congestion (Moorcroft, 2003). Often, these medications are effective at relieving symptoms of the conditions for which they were prescribed, yet side effects may include impacts on the sleep/wake cycle. Often, concomitant with this reduced sleep quality is an awareness of more pain or discomfort, thus creating a negative cycle.

Sedative-hypnotics, or sleeping pills, also may affect the sleep cycles. In hopes of being able to fall sleep faster or maintain sleep periods without disruption, many individuals who experience pain, stress or interrupted sleep turn to sleeping pills to compensate for any lost sleep or sleep that they feel they are unable to acquire naturally. Three classes of drugs currently are approved for treatment of insomnia, including the non-benzodiazepines (e.g., zolpidem), the benzodiazepines (e.g., temazepam), and a melatonin receptor agonist (i.e., ramelteon) (Schenck, 2008). In addition, dietary supplements and herbal remedies (e.g., kava and valerian) are commonly utilized, yet their lack of regulation by the Food and Drug Administration (FDA) indicates a general lack of standardization relative to dosages and manufacturing. Schenck (2008) noted that the FDA-approved classes of drugs approved for the treatment of insomnia are a helpful component of sleep therapy treatment, given that patients are appropriately diagnosed and are followed routinely. For instance, Schenck (2008) listed the rapid absorption, the dearth of active metabolites, the relatively low potential for abuse or side effects, the extensive research basis and his personal clinical experience with the non-

benzodiazepines in support of their use, alongside talk therapy, in the treatment of individuals with insomnia.

Acknowledging their utility in a short-term context with certain populations, Naiman (2006), on the other hand, underscored the many factors that contribute to the overuse and abuse of sleeping pills within society. Among others, the misinformed belief that sleep is synonymous to unconsciousness augments the desire of individuals to knock themselves out with what Naiman (2006) referred to as *magic bullet pills* (i.e., sleeping pills). Disregarding the intricacies of the sleep/wake cycle, the benefits gained from cycling through each of the respective sleep stages in a natural way, as well as the lifestyle factors, cognitions and underlying anxieties that are sustaining sleeping problems, humans in need of fast fixes are quick to undermine their own autonomy. Rather than follow their own circadian cycle or make the effort to discern which lifestyle factors are hindering their sleep, they seek these sleeping aides. Unfortunately, “most [sleeping pills] are more like the scatter of shotgun pellets that take broad aim at wakefulness but simultaneously hit and damage deep sleep and dreaming in the process” (Naiman, 2006, p. 85). In addition to the residual drowsiness and cognitive impairments often experienced in the next waking period, many sleeping pills increase time spent in the lighter, stage II sleep and reduce time spent in SWS and REM sleep (Naiman, 2006). Natural sleep with the appropriate allocation of time spent in each stage is therefore not restored with these pills; a state of unconsciousness is simply induced (Naiman, 2006). Awakenings may still occur, yet patrons often feel like they awakened less on account of their amnesia for the events. Dependency, habituation, and rebound effects are all

common as well (Naiman, 2006). Further, Naiman (2006) eloquently argued that the overarching problem with sleeping pills is their attempt to cure sleeping ills without due consideration of the individual's holistic life context. Biological and psychological factors, internal rhythms, and lifestyle choices are disregarded.

In summary, sedative-hypnotics may be appropriately or inappropriately utilized by individuals desiring to acquire more sleep. Either way, the body on sedative-hypnotics during sleep is different from the same body free of sedative-hypnotic metabolites during sleep.

Illness also affects sleep patterns. When illness is looming, the desire to sleep increases, often serving as an advanced warning that the body is combating an infection (Moorcroft, 2003). Depending on the type of bacteria, the nature of the host's current immune system, and the point of entry of the respective bacteria, many changes in sleep may be anticipated during a bacterial infection. As bacteria enter the host, white blood cells (i.e., macrophages) assail and engulf the bacteria then subsequently excrete certain chemical components (i.e., muramyl peptides) that were actually part of the cell walls of the bacteria (Moorcroft, 2003). The release of these peptides initiates biochemical processes that precipitate fever, immune responses, and increased levels of cytokines (e.g., interleukin-1B) (Moorcroft, 2003). These cytokine levels constantly play a role in sleep, as the body is always combating bacteria that is present in the gastrointestinal tract, yet they are simply elevated when more bacteria enters the host (Moorcroft, 2003). As these cytokine levels increase, feelings of sleepiness and levels of NREM sleep increase, while the amount of REM sleep decreases. Specifically, levels of SWS and delta waves

increase around the height of, and immediately following, the infection, followed by significantly lower levels a few days later (Moorcroft, 2003). Infections caused by fungi, viruses or protozoans precipitate similar effects. Although more research is warranted as to the specific function of these sleep changes surrounding illness, Moorcroft (2003) stated it is probable that the additional amounts of SWS permit the allocation of more resources to healing and the febrile state and to the reduction of the swell of infection.

Sleep deprivation. Regardless of the specific etiology, depriving subjects of a sleep state has ramifications. Constant, sustained deprivation of deep sleep in animals leads to illness and ultimately death (Naiman, 2006), further underscoring the strong relationship between sleep and health. Unfortunately, even multiple nights of partial sleep deprivation will lead to effects that resemble total sleep period deprivation and a subsequent vengeful rebound of sleep. Although recovery from sleep deprivation can be achieved in a fairly fast and efficient manner, the characteristics of sleep in nights following such deprivation will be altered (e.g., higher sleep efficiency and more REMS earlier in the night (Moorcroft, 2003). Those who continue to struggle to achieve restorative sleep may experience a plethora of side effects. The salience of these sleep deprivation effects may ebb and flow, depending on numerous factors, such as environmental stimuli, reinforcement, and ingestion of substances that attenuate the effects, yet the intensity of the numerous impacts of sleep deprivation will continue to increase as the level of sleep deprivation rises (Moorcroft, 2003). Moorcroft (2003) described these widespread effects and categorized them as behavioral, biological, cognitive, and subjective.

Among others, the biological impacts of sleep deprivation may include itchy eyes, tremors, weight gain, a decrease in body temperature, droopy eyelids, heart palpitations, alterations in hormone levels, and a significant impact on immune system functioning (Moorcroft, 2003). Haack, Sanchez, and Mullington (2007) investigated the relationship between sleep deprivation, pain, and inflammation in a randomized, 16-day controlled in-laboratory study. By randomizing 18 volunteers to either 12 consecutive days of sleeping eight or four hours per night, Haack et al. (2007) were able to examine the effects of reduced sleep duration on peripherally circulating inflammatory mediators and the relationship between the degree of inflammation and the increase in level of pain following reductions in sleep periods. Throughout the experiment, participants completed measures related to their mood, tiredness-fatigue, and pain symptoms, while the experimenters collected periodic blood and urine samples to assess levels of plasma interleukin (IL)-6, serum C-reactive protein (CRP), metabolites D2 and E2, plasma soluble tumor necrosis factor receptor p55 (sTNF-R p55), and urinary levels of prostaglandin (PG). Haack et al. (2006) found IL-6 levels were significantly elevated in the four hour sleep condition group relative to the eight hour condition ($p < 0.05$), and these elevated IL-6 levels were strongly associated ($r = 0.67$; $p < 0.01$) with greater pain ratings following sleep period reductions. Tiredness or fatigue did not better account for these findings. The researchers concluded that significant reductions in sleep cause elevations in IL-6 levels that, in turn, facilitate or augment pain levels. In individuals with existing diagnoses or disorders, these reductions in sleep alone may maintain

increased pain and inflammation levels (Haack et al., 2007), therefore making sleep an appropriate area to target for symptom reduction interventions.

Additionally, sleep deprivation may lead to a subjective sense of lethargy, anhedonia, irritability, paranoia, negative mood and a sense of loss of control (Moorcroft, 2003). Cognitive impacts of sleep deprivation also are apparent, and examinations of functional imaging of the brain demonstrate differences in patterns of brain activity following deprivation (Moorcroft, 2003). Relative to mental impacts of sleep reduction, the following may be prevalent: impairments in concentration, reductions in reaction times, short term memory capacity, mental flexibility, integrative ability and originality, increased indecisiveness, perceptual distortions or hallucinations, impairments in logical reasoning in the context of complicated problem solving, and blunders in consciousness (Moorcroft, 2003; Schenck, 2008). Likewise, Caplette-Gingras, Savard, Ivers, and Savard (2009) reported significant impairments in episodic memory in breast cancer patients with insomnia treated with chemotherapy, radiation therapy or surgery and actively receiving hormone replacement therapy relative to breast cancer patients with similar treatments yet who are considered good sleepers ($F(1,64) = 7.68, p < 0.01$). Sleep deprivation appears to impact to a greater extent tasks requiring mental effort, rather than those demanding strictly physical effort (Moorcroft, 2003), yet physical tasks may *seem* more difficult and demanding with sleep deprivation. Behaviorally, sleep deprivation may lead to clumsiness, reduced psychomotor abilities, reduced vigilance and spontaneity, less of a drive to socialize and microsleeps (i.e., brief lapses of attention that occur more frequently as level of sleep deprivation increases) (Moorcroft, 2003).

Without external reinforcement or stimulation, these microsleeps occur more frequently, leading to brief lapses during the respective activity that is occurring at the time. If these microsleeps occur during high risk activities (e.g., driving), the ramifications can be severe.

This brief review of the potential implications of sleep deprivation highlights its potentially severe and far-reaching implications. In a population whose members are already struggling with numerous life and physical hurdles (such as cancer patients), more challenges may be confronted when trying to enter and maintain the sleeping state, and the impacts of such sleep deprivation may be even more devastating. A review of the sleep quality of cancer survivors will highlight what is known about the sleep of these individuals.

Sleep Quality of Cancer Survivors

Many medical conditions are associated with irregularities in sleep that may, in turn, heighten the perceived severity of the symptoms of the medical condition (Parish, 2009). Numerous researchers have examined the prevalence of disruptions in the sleep/wake cycle in cancer patients in particular. In a systematic assessment, Berger et al. (2007) reported that 30-50% of adults with cancer have sleep disorders- a prevalence that is two times that of the general population. Kozachik and Bandeen-Roche (2008) reported that pain, fatigue and insomnia are some of the most widespread, distressing, and undermanaged symptoms that cancer patients experience. In an investigation of 752 cancer patients from three states who had been given a diagnosis of one of the ten most common cancers, Baker et al. (2005) found that 47.9% of participants reported

experiencing sleep difficulties, while 67.1% reported reductions in strength and fatigue (more noticeable in those who received chemotherapies). Parish (2009) noted that those who are currently receiving or recently completed therapies for cancer treatment often experience numerous nighttime awakenings, insomnia, extreme fatigue and hypersomnolence. Weinhouse and Schwab (2006) described the sleep of critically ill patients as severely fragmented, riddled with more awakenings, and consistent of more stage I sleep, rather than stages II, III, IV and REM sleep. Likewise, the total hours of sleep per nycthemeron may approach that of healthy individuals, yet these hours are typically more parceled throughout the day and night by means of periodic napping (Weinhouse et al., 2006). Numerous factors, including their medical illnesses, psychological stress, immediate surroundings (e.g., the lights, noises, and constant tending characteristic of the intensive care unit), medications and treatments may have contributory roles in this reduced sleep quality.

Similarly, Kvale and Shuster (2006) noted that a cancer diagnosis and treatment place survivors at an increased risk for disruption of the sleep/wake cycle. Specifically, behavioral disruptions of one's normal routine (e.g., more time in bed or in the hospital, less daytime activity) increase the odds of disruption in the sleeping cycle; discomfort, physical symptoms and pain often combine to impact sleep onset and maintenance; reduced lung capacity or neoplasms may impact respiratory functioning; symptoms of depression or anxiety may serve as additional psychosocial concerns and sources of stress; and individuals who are immune-suppressed as a consequence of advanced disease or treatment may have organic disruptions of their sleep/wake cycles as well (Kvale &

Shuster, 2006). As more individuals survive cancer and live with pathologic and treatment effects, the importance of pinpointing, targeting and even preventing all lingering effects, including sleep disruptions, becomes all-the-more important (Baker, Denniston, Smith, & West, 2005). With a primary focus of quality of any remaining life in palliative medicine (Kvale & Shuster, 2006), sleep disruptions have implications that are too vast to be ignored.

In a recent study, Fernandes, Stone, Andrews, Morgan, and Sharma (2006) compared the sleep disturbances, fatigue, and circadian rhythms in 25 female cancer patients with those of 25 healthy controls by means of subjective (i.e., self report instruments) and objective (i.e. wrist actigraphs, or “small piezoelectric accelerometers that are worn on the wrist...[to] detect movement of the limb and then summarize the data in 1-minute epochs” (p. 247)) measures. Compared to the healthy controls, cancer patients tended to be less active during the day, more active at night, have less marked circadian rhythms, more fatigue, poorer sleep quality and overall lower quality of life (Fernandes, 2006). All actigraphic parameters (i.e., mean activity levels, sleep periods, sleep efficiency, sleep latency, and awakenings after onset), with the exception of sleep latency, were significantly different between the patients and controls as well. Within the cancer group, estimates of fatigue were associated with reductions in QOL, self-reported physical functioning, constipation and depression. In their small sample, Fernandes et al. (2006) concluded that, relative to controls, many cancer patients have both verifiable impairments in sleep and changes in circadian rhythms that can potentially lead to QOL impairments.

Savard and Morin (2001) underscored the prevalence and general neglect of one sleeping problem in particular, insomnia, within the cancer population. Finding that symptoms of insomnia are prevalent in the two to five years following treatment, Savard and Morin (2001) concluded that symptoms of insomnia develop a chronic course in a large percentage of cancer survivors. The etiology of these symptoms may be classified as predisposing factors (i.e., existing traits that increase an individual's likelihood of developing insomnia, such as aging, the presence of a psychiatric disorder or a familial history of insomnia), precipitating factors (i.e., contextual conditions that lead to the onset of insomnia), and perpetuating factors (i.e., variables that contribute to the maintenance of symptoms) (Savard & Morin, 2001). When reviewing many studies, it is difficult to discern whether symptoms of insomnia are the manifestation of variables that were already in existence prior to the cancer diagnosis or treatment (i.e., predisposing factors), or whether the sleep/wake disturbances truly originated following the cancer diagnosis or treatment (i.e., precipitating factors). Such precipitating factors that may be associated with insomnia in a cancer-context include psychological reactions to the diagnosis itself, physical effects of the various oncologic treatments, hospitalization, pain, effects of medications, and delirium, among others (Savard & Morin, 2001). The presence or absence of perpetuating factors within this population (e.g., chronic pain, maladaptive beliefs about sleep or poor sleep hygiene) will then determine if this insomnia becomes a chronic problem. Of those who experience chronic insomnia, many report that their inability to sleep negatively impacts their ability to cope with stress,

emotionality, concentration, sense of physical wellness, and their daily functioning (Parish, 2009).

It is apparent, then, that vast numbers of cancer patients struggle with sleep disturbances and disorders. Yet these disruptions often are not the focus of targeted interventions (Berger et al., 2007). Interestingly, Homsí et al., (2006) reported that patient reports and patient assessments do not always yield comparable results. Specifically, while controlling for race, gender and age, Homsí et al. (2006) found that the median number of symptoms identified via the systematic assessment of patients was ten times higher than the number of symptoms volunteered by the same patients ($p < 0.001$). Specifically, within a sample of 265 patients who were referred to the palliative medicine department, 322 symptoms were volunteered, while an additional 2075 symptoms were pinpointed via systematic assessment. While pain was volunteered the most, fatigue was the symptom most commonly identified by systematic assessment (Homsí et al., 2006), suggesting an underreporting of specific types of symptoms. Overall, insomnia was one of the ten most common symptoms within this sample. Interestingly, only 2.5% of the participants readily volunteered concerns related to insomnia. When systematically assessed, 40.5% revealed that they were struggling with insomnia (Homsí et al., 2006). Relative to bad dreams, 1.0% voluntarily revealed that they were experiencing bad dreams, while 6.0% revealed this problem when assessed systematically. Homsí et al. (2006) concluded that some symptoms are more likely to be volunteered than others, and a thorough assessment is necessary for a detailed understanding of the patient's status. It seems, then, that concerns related to sleeping are

prevalent within the cancer population, yet patients may not readily volunteer these concerns. It is possible that patients believe that other concerns are more salient or pressing relative to their medical health. Accordingly, systematic assessment of sleep-related concerns may be needed (Homsí et al., 2006).

This adequate assessment of sleep disturbances and sleep quality does not occur, however, with only one question or one sleep parameter (Berger et al., 2007). In other words, while measurement may take many forms, including those that are objective (e.g., wrist actigraphs or polysomnography) or subjective (e.g., self report, sleep questionnaires, sleep scales on QOL questionnaires or sleep diaries) in nature, accurate measurement of sleep disturbance and sleep quality must be multidimensional (Berger et al., 2007). Although disagreement exists as to what these parameters should definitively be (Berger et al., 2007), professionals concur that there should be many holistic dimensions accounted for in this assessment.

Unfortunately, in a systematic review of current methodological approaches utilized to study sleep disturbances in adults with cancer, Berger et al. (2007) did not find many studies in which the researchers were compliant with these suggestions. Specifically, Berger et al. (2007) systematically searched for studies (descriptive or interventional in nature) written in English between January 1, 1995- January 30, 2005 in which the longitudinal collection of both sleep and QOL data (a minimum of two time points) in adult cancer patients by means of psychometrically sound instruments were detailed. Of the 40 studies that met their inclusion criteria, only four utilized a multi-item sleep-specific instrument, and only six employed more than a single item to assess sleep.

Many studies considered sleep to be a secondary or ancillary analysis. These findings elucidate the low methodological quality of many sleep studies and the general infantile state of this collective body of research in general (Berger et al., 2007). Single item questions related to sleep insufficiently assess and capture the quality of this intricate process or its associated effects (Berger et al., 2007; Fernandes et al., 2006).

Many other variables in combination may serve to keep sleep disturbances from being assessed and included in interventions. Many patients may not believe that sleep-related concerns are true medical conditions or worth the precious discussion time at a doctor visit. Likewise, many medical doctors may feel ill equipped to broach the subject or may lack sufficient time to comprehensively assess the nature of their patients' sleep. Sleep-related concerns and their vast implications may then go untreated, further complicating the healing process. Collectively, the aforementioned reviewed findings reveal that sleep disturbances and the connected impediments are among the most common symptoms experienced by cancer patients during all phases of care, yet they have traditionally received minimal attention and few efforts at targeted improvement from clinicians and researchers within the oncology community (Berger et al., 2006; Savard & Morin, 2001).

Sleep quality of CS+HIPEC recipients. The sleep quality of CS+HIPEC recipients has received even less attention from researchers. In a review of the literature regarding members of this population, only one article was located that focused on a concern potentially related to sleep impairment. Anderson and Hacker (2008) explored the literature and hypothesized potential contributing factors to fatigue within women

with stage III or IV ovarian cancer who are receiving intraperitoneal (IP) chemotherapy. In addition to surgical variables, the effects of the IP chemotherapy, pain, anemia, gastrointestinal disturbances and emotional distress, Anderson and Hacker (2008) stated that sleep disturbances may be precipitating factors for fatigue. It is important to note, however, that no empirical studies of sleep quality among CS+HIPEC patients were located. To better understand the true sleep disturbances and their ancillary effects within this population of CS+HIPEC recipients, more assessment and data collection needs to occur.

In conclusion, sleep is an essential process that provides important biological and psychological benefits to its host. Unfortunately, individuals with chronic illnesses, including cancer patients, remain sleep deprived on account of the combination of biological, physiological, medicinal, environmental or psychological factors. A paucity of investigators have examined the multidimensional construct of sleep quality in cancer patients, and even fewer have examined sleep quality in survivors of CS+HIPEC. Without such descriptive data, it remains unknown what components of sleep quality are most affected in those who had CS+HIPEC, and without this understanding, targeted sleep-related interventions are not possible. Without such psychosocial interventions or adjustments, sleep disturbances may become chronic, and other diagnosis- or treatment-related concerns may be exacerbated.

In summary, patients post-CS+HIPEC may be confronting treatment-related toxicities, sleep quality impairments, and/or adjustments in any number of dimensions of QOL. A better understanding of how the aforementioned variables are interrelated can be

acquired with the support of a suitable biopsychosocial conceptual model of patient outcomes, such as the Wilson and Cleary model (Wilson & Cleary, 1995). In this model, variables from a traditional biomedical model and those from a social science paradigm are combined so as to integrate these differing models of health and offer causal relationships between biological, psychological, and social variables (Wilson & Cleary, 1995).

The Wilson and Cleary Model

Patient outcome measures may take a plethora of forms in the weeks, months, and years post-CS+HIPEC. For example, a CS+HIPEC survivor's health team will likely be interested in outcome measures pertaining to white blood cell counts, hemoglobin levels, and surgical wound appearance (i.e., biological and physiological outcomes), the number of bowel movements or episodes of emesis and the presence of any depressive or anxious symptoms (i.e., symptom status), the patient's ability to ambulate and shower (i.e., functional status), and even her or his own perception of how he or she is faring (general health perception), among many others. By training, individual members of a patient's multidisciplinary health team often focus on and prioritize one particular category of these outcome measures, yet each category of measure has important implications for the CS+HIPEC survivor and her or his current health and quality of life. Likewise, these underlying variables represented by outcome measures have causal and bidirectional influences on one another, underscoring the need to be cognizant of the impact that variables in one category may have on those of another (Wilson & Cleary, 1995). Mental health professionals in any setting are trained to think systemically, looking for

relationships, patterns, and activating events in their patients' lives. Arguably, such interrelationships between levels of patient outcomes are highlighted optimally in patients within a medical setting when changes in biological or physiological variables all-too-often result in symptom reports, impairments in functional status, the development of mood disorders, and ultimately a reduced rating of one's quality of life. The positive side of these interrelationships between levels of patient variables is revealed, however, when interventions designed to target one level of patient outcomes results in a contagion of improvement across the remaining levels. Not surprisingly, mental health professionals transitioning into medical settings initially may find this need to broaden their clinical conceptualizations and research investigations to include biological or physiological variables in addition to the staple psychological and social variables quite challenging. If the primary goal of clinical care is to improve the overall outcomes and QOL of patients, however, diagnoses and interventions designed to improve these outcomes optimally should be built upon a solid conceptual understanding of the causal conduits that network the various classifications of patient outcomes (Wilson & Cleary, 1995). In this investigation, consideration is given to the impact of an array of variables, from those that are biological and physiological to those psychosocial in nature, on survivors' long-term QOL.

Given the numerous relationships that exist between traditional clinical (i.e., biomedical) variables and measures of health status (e.g., QOL measures), it is interesting that these associations are not well articulated in the existing integrative models and theories of patient outcomes (Wilson & Cleary, 1995). In response, Wilson and Cleary

(1995) created a conceptual model that illustrates the relationships of levels of clinical variables to such end measures of health-related QOL. Specifically, these researchers combined variables from a traditional biomedical model with those from a social science (QOL) model in order to create an integrative model that classifies patient outcome measures by means of the basic health concepts they represent. Concurrently, Wilson and Cleary (1995) illustrated suggested causal relationships between these levels of measures. The measures of health are conceptualized as existing on a hierarchical continuum, with biological and physiological measures on one end and increasingly integrated and compound measures, such as general health perceptions, on the other end. If one is going to gather QOL information with the end goal of understanding the population and creating interventions to target problematic areas, a solid understanding of the relationships between the many levels of patient outcome variables is essential so that the interventional efforts are appropriately targeted. The Wilson and Cleary Model (1995) provides a framework for understanding these relationships between patient outcome measures that assess concepts that are relatively easy to define and appraise (e.g. hemoglobin level) and those that are inherently more difficult to define and compute (e.g. overall QOL). This taxonomy of patient outcome measures commences with measures pertaining to cell counts or single organ function and continues on to those examining an individual in a systemic context.

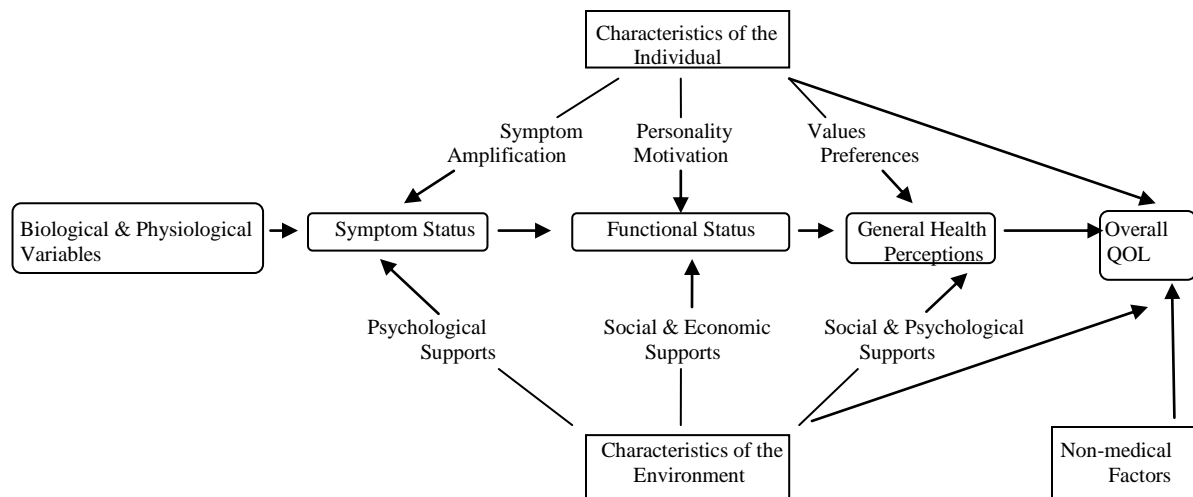


Figure 1. Wilson and Cleary's conceptual model (1995) of patient outcomes.
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Prior to examining the Wilson and Cleary Model (1995) in depth, an examination of the two models that were integrated into this one conceptual model serves to underscore respective strengths as well as the divergent foci and principles of each. With its foundation in biology, physiology and biochemistry, the traditional biomedical model was created in order to investigate the underlying cellular, genetic and molecular disease mechanisms (Wilson & Cleary, 1995). Etiologic agents, processes of pathogenesis, as well as physiological, clinical and biological outcomes are the foci (Wilson & Cleary, 1995). Primarily via controlled experiments, the predominant goal of those espousing this model is to better comprehend causation in order to direct both diagnosis and treatment. On the contrary, with its roots in psychology, sociology and economics, the social science (QOL) model focuses on dimensions of functioning, overall well-being, and the ways that institutions and social systems impact individuals (Wilson & Cleary,

1995). Researchers utilizing this model attempt to find ways to precisely measure composite feelings and behaviors, and genuine experimental designs are much more difficult to implement comparatively (Wilson & Cleary, 1995).

When combining the biomedical and social science models, Wilson and Cleary (1995) had many aims, the first being the inclusion and categorization of measures of patient outcomes representing variables from both of the aforementioned models. Secondly, by illustrating the relationships between these outcome measures that target different classes of variables, the researchers hoped to elucidate causal pathways between variables, thereby informing conceptualization, diagnosis, treatment, and interventions. If social science researchers are gathering QOL data, for instance, the numerous pathways of patient variables impacting these QOL scores should be understood. Finally, Wilson and Cleary (1995) desired to create an empirically testable model that is sensible and user-friendly for clinicians and researchers alike.

In the model, the measures of health are depicted on a continuum of increasing complexity. Patient outcome measures representing each of the five categories within the model will be collected in this dissertation. On the far left side are the biological measures, while the increasingly integrated measures, such as general health perceptions and QOL, are represented on the right (Wilson & Cleary, 1995). Arrows represent the *dominant* causal associations, yet the absence of an arrow between outcome measure categories does not denote an overall lack of a relationship nor does it denote that the relationship is strictly unidirectional. Rather, bidirectional and additional relationships beside those depicted pictographically exist as well (Wilson & Cleary, 1995). A total of

five levels of patient outcome measures are portrayed in the model. Additionally, characteristics of both the individual and the environment have the potential to impact measures from each level of the model. These factors are therefore discussed separately.

Level one consists of *biological and physiological variables* (Wilson & Cleary, 1995). Although the model developers noted that molecular and genetic factors are the most basic health status determinants, they decided to make biological and physiological variables the initial level of the model, as these are the variables most routinely considered and measured in daily clinical work. Measures pertaining to this category provide evidence of the current functioning of the cells, organs, and organ systems within an individual (Wilson & Cleary, 1995). Examples from this level that are pertinent to CS+HIPEC survivors include laboratory results (e.g., complete blood cell counts, blood gas levels, microbial levels), measures of physiological function (e.g., blood pressure readings), or diagnoses (e.g., ovarian cancer with peritoneal metastases). Specific variables from this category that will be used in the analyses for this dissertation include age at CS+HIPEC, primary diagnosis, and surgical resection status. In terms of measurement, these patient outcomes are the most straightforward and the easiest to measure without the impact of intervening variables.

In level two, *symptom status*, the focus broadens from the cells or specific organ systems to the holistic individual (Wilson & Cleary, 1995). Given that many categories of symptoms exist (including psychological, physical, and even bio-psychological symptoms), Wilson and Cleary (1995) broadly defined a *symptom* as “a patient’s perception of an abnormal physical, emotional, or cognitive state” (p. 61). By the time an

individual visits a clinician to report a symptom, numerous processes heavily influenced by social, cultural, familial, and personal factors, have already occurred, including perception of and judgment about the symptom. “Symptom reports, therefore, are expressions of subjective experiences that summarize and integrate data from a variety of disparate sources,” (p. 61) noted Wilson and Cleary (1995). Inherent complexity therefore exists between level one (i.e., biological and physiological) and level two (symptom status) variables. For instance, some severely atypical level one variables may go unreported by some people, while others present with intense symptom reports with no notable level one variables (Wilson & Cleary, 1995). Given this complex, often inconsistent, relationship between biological or physiological variables and symptom reports as well as the additional non-clinical factors likely impacting this relationship, Wilson and Cleary (1995) suggested that targeting presumed underlying level one variables will not always reduce or altogether remove symptom reports. Clinicians and researchers must examine the other variables potentially impacting these level two reports. Some examples of outcome measures of interest in this dissertation in the symptom status category include sleep quality and the bodily pain (BP) subscale scores.

Level three in the model is *functional status*. Measures pertaining to this level capture the ability of an individual to perform a specified task (Wilson & Cleary, 1995). Typically, numerous facets of functional status are assessed in these measures, including physical, role, social, and psychological functioning (Wilson & Cleary, 1995). Not surprisingly, level one and level two variables are usually associated with level three variables. Likewise, the impact of biological and physiological (level one) variables on

functional status (level three) is often mediated by symptom status (level two). However, these relationships are not exclusively explained by these three categories of variables (Wilson & Cleary, 1995). Personal and environmental variables also have contributory roles to this functional status. Further research is needed to elucidate alternate mediating variables (Wilson & Cleary, 1995). Pertinent functional status outcome measures in this dissertation include scores on the role emotional (RE), role physical (RP), and social functioning (SF) subscales as well as the ECOG performance status scores assigned to patients by the surgeons.

The next level in the Wilson and Cleary Model (1995) is *general health perceptions*. General health perceptions are, by nature, subjective and represent a general integration of all of the preceding levels of health concepts, in addition to many others (Wilson & Cleary, 1995). Because of the numerous variables that contribute to one's health perceptions, a gamut of health perceptions often are noticeable among individuals with the same general symptoms, functioning, and overall health status. The general health (GH) QOL subscale score utilized in this dissertation is an outcome measure that falls neatly within this category.

Finally, level five of the model consists of patient outcome measures examining *overall QOL*, such as the overall QOL scores obtained from participants by means of the SF-36 in this dissertation. Similar to general health perceptions, QOL measures are increasingly complex and difficult to dissect, given the large number of variables impacting one's perception of her or his QOL. Additionally, given the adaptability of individuals and their tendency to alter both expectations and goals based on changing life

circumstances, QOL outcomes may vary over time simply as a consequence of a shift in perception (Wilson & Cleary, 1995). In summary, although associations exist between variables represented by the five levels of this model, numerous other intervening or confounding variables that cannot be controlled by the clinician or system must be considered as one transitions further to the right of the model (Wilson & Cleary, 1995).

In addition to the five levels of patient outcomes, characteristics of both the individual and the environment also are depicted in the model (Wilson & Cleary, 1995). Characteristics of the environment that purportedly impact variables at certain levels of the model are psychological, economic, and social supports. Characteristics of the individual delineated by Wilson and Cleary (1995) include symptom amplification, personality, motivation, values, and preferences. To illustrate the role of patient preferences, Wilson and Cleary (1995) noted that certain symptoms may be preferable relative to others for any given individual, and their presence may largely impact general health perceptions or QOL (Wilson & Cleary, 1995).

Finally, not only do psychological and emotional factors have an important role in *each* level of the model (Wilson & Cleary, 1995), but, based on the conceptualization of the researcher or clinician and the measure selected to assess the respective psychological factor, psychological or emotional variables can be categorized under numerous levels of this five-level model. For instance, a psychological symptom may be considered a biological or physiological variable (level one); if a researcher is utilizing a symptom measure to assess symptoms of a psychological concern, symptom status (level two) might be a more appropriate categorization; or if the researcher is administering a scale

that assesses functioning as a consequence of the psychological concern, the measure may be considered one of psychological functioning (level three) (Wilson & Cleary, 1995). It is this fluid and overarching impact of psychological factors that convinced Wilson and Cleary (1995) not to house these factors in one discrete level within the model. In conclusion, even though they are not represented with their own level in this model, psychological and emotional factors have the potential to have strong, bidirectional associations and causal relationships with variables at each of the five levels of the model (Wilson & Cleary, 1995).

The Wilson and Cleary Model (1995) is useful in both research and clinical work involving CS+HIPEC patients. From a research standpoint, the Wilson and Cleary (1995) conceptual model informed the design of this investigation and the selection of the variables, constructs, and instruments. Specifically, by using the model as a framework to unpack the contributions of and causal relationships between the many levels of patient outcomes in the context of QOL reports, the investigator was able to make informed selections relative to important variables of measurement. The specific variables of interest within the study can be classified into numerous levels across the taxonomy, from level one to level five, and the model may have explanatory value relative to the end results.

This integration of outcome measures from varying model categories is illustrated in various research questions within the dissertation. For example, the researcher is interested in the respective contributions of age at CS+HIPEC and surgical resection status (biological or physiological variables) in predicting QOL (the level five, integrative

variable) within each of the primary diagnostic groups (biological variable). Relying on the model, one can comprehend how variables from intervening levels of patient outcomes (i.e. symptoms, functional status, and the patient's perception of her or his health) may mediate this relationship and how characteristics of the patient or the patient's environment may augment or diminish the strength of these hypothesized relationships. As an additional example within the proposed study, sleep quality will be examined in relation to QOL. From the model, one can extrapolate that (if categorized as an outcome measure pertaining to symptom status), not only should they be related, but variables pertaining to functional status (e.g., impaired daytime functioning) and general health perceptions may mediate this relationship (Wilson and Cleary, 1995). Likewise, characteristics of the respective patient and the patient's environment likely influence these relationships.

In the clinical context with CS+HIPEC survivors, reliance on the conceptual model informs systemic thinking and multidisciplinary collaboration, as variables in each level of the taxonomy have implications for those in alternate levels and ultimately impact overall QOL scores. Likewise, the model highlights the ways that specific characteristics of the individual and the individual's environment impact variables in each category, encouraging the clinician to include unique patient variables into the conceptualization. A personally-suited, in-hospital psychosocial intervention, for example, may serve as the impetus for change across the taxonomy of patient variables. Following individual counseling, a CS+HIPEC patient may report improved mood, fewer depressive symptoms and a lower perception of pain. Subsequently, he may begin

ambulating and showering, thereby using his muscles, experiencing fewer back sores from remaining sedentary, and even socializing occasionally while walking the halls. As he slowly begins using his body, he achieves more restorative sleep at night, during which his body is able to devote more energy to healing. As these subtle improvements accumulate, the patient begins reporting enhanced health perceptions and ultimately improved quality of life. By relying on this conceptual framework, the clinician adopts a systemic viewpoint to consider how various levels of patient outcomes impact her or his targeted variable of interest and may ultimately provide enhanced, holistic clinical care. If supported by empirical data, such interventions could serve as the applied end of this line research.

In conclusion, the Wilson and Cleary Model (1995) is an important biopsychosocial addition to clinical work and research within a setting in which health related QOL is of importance. It is conceptually suitable to research and clinical work with CS+HIPEC survivors, accounting for the many levels of variables potentially contributing to overall QOL (as measured by the SF-36 in this dissertation). Incorporation of this conceptual model can inform diagnosis, treatment, and interventions, as outcome measures pertaining to numerous levels of variables from both the traditional biomedical model and the social science, QOL, model are integrated. Likewise, the suggested relationships between these variables permit practitioners to better understand the overall QOL impact of interventions designed to target variables at one of the lower levels in the model (Wilson & Cleary, 2005).

Limitations of Research on QOL in Survivors of CS+HIPEC

It is evident that reliance upon a conceptual model such as the Wilson and Cleary (1995) Model can serve to enhance a practitioner's interpretation of information retrieved from patient outcome measures. An additional means of capitalizing upon any retrieved patient outcome information is to ensure the methodological integrity of the research. Following a review of the QOL studies pertaining to CS+HIPEC survivors, some thematic limitations are apparent. In their recent review of studies pertaining to HRQOL and CS+HIPEC, McQuellon and Duckworth (2009) underscored many of these limitations in hopes that they will be considered in future studies.

For starters, only nine studies in which QOL data of CS+HIPEC survivors were gathered were retrieved in the literature search for this dissertation. Within these studies, sample sizes were small, thereby limiting generalizations (McQuellon & Duckworth, 2009). For example, a total of three cross-sectional studies performed with long-term survivors were located. McQuellon et al. (2003) reported a sample size of 17 out of a potential 109 patients treated between January of 1992 and December of 1997, while Schmidt et al. (2005) had a sample size of 20 out of a possible 67 patients treated between March of 1995 and February of 2003. With such small numbers, the power of analyses performed is weakened, thereby warranting caution upon the interpretation of any results. In the third, and most recent, cross-sectional study located, Zenasni et al (2009) reported a sample size of 68, reflecting significant improvement relative to sample size. Within the description of their inclusion and exclusion criteria, however, Zenasni et al. (2009) stated that all individuals with recurrent disease or comorbidities were

excluded from participation. The participants in the Zenasni et al. (2009) study, then, represent strictly the healthy individuals and the best-case scenarios. These inclusion criteria must be considered upon the interpretation of their results.

Similarly, sample sizes from the longitudinal studies are relatively small as well. McQuellon et al. (2001) commenced their study with 64 participants (baseline), reducing to 48 (post-procedure), 41 (three months), 39 (six months), and 31 (12 months). A total of 23 individuals completed all instrument batteries across the time series (McQuellon et al., 2001). In 2007, McQuellon et al. retrieved baseline assessments from 96 persons and had 12-month data from only 24 persons. In alternate longitudinal studies, Tuttle et al. (2006) reported a sample size of 35, while Jess et al. (2008) maintained a sample size of 23. These small sample sizes reflect high mortality rates, high attrition rates (presumably due to recurrence or other complications), and a plethora of missing data, again limiting generalization and the power of any analyses.

The missing data from these studies are likely not missing at random (McQuellon et al., 2007). It is probable that those with the most significant illnesses and debilitating symptoms drop out of the research studies. Of these dropouts, a significant percentage is likely experiencing significant psychosocial symptoms (McQuellon et al., 2007).

Additionally, individuals who die prior to discharge from the hospital or before the first post-procedure assessment likely do not contribute their experiences to the data pool.

This lack of randomness likely associated with missing data suggests that existing datasets represent the best-case scenarios. Those who share their stories are those who are living and living without symptoms that prevent them from completing a packet of

questionnaires. McQuellon et al. (2007) suggested the need for CS+HIPEC researchers to design studies that permit the investigation of those patients who drop out or who have significant psychosocial stressors or QOL impairments associated with the treatment or recurrent disease. In other words, these researchers reminded colleagues of the importance of studying those who do not fare well post-CS+HIPEC.

Next, the timing of both baseline and post-procedure instrument administration varies between the studies located (McQuellon & Duckworth, 2009), introducing a possible source of variance between the sets of data. On the front end of the longitudinal studies retrieved, baseline data acquired one week versus one day pre-CS+HIPEC may vary markedly in nature. Relative to post-procedure administrations, McQuellon et al. (2007) administered surveys at baseline and three, six, and 12 months post-procedure; Alexander et al. (2003) administered surveys at baseline and six weeks, three, six, and nine months post-procedure; while Tuttle et al. (2006) retrieved data at baseline and four, eight, and 12 months post-procedure. Data collected at differing time post-CS+HIPEC limits comparisons across studies.

McQuellon and Duckworth (2009) noted the considerable morbidity experienced in the acute recovery phase following surgery yet the few incidences when data have been collected during this sensitive time period when patients are experiencing so many hardships. For example, both McQuellon et al. (2001) and Alexander et al. (2003) gathered data within the six weeks post-procedure, and both noted significant QOL reductions relative to baseline. In contrast, Tuttle et al. (2006) refrained from gathering post-surgery data until four months post-procedure. Their baseline and four month

assessment results were very similar, not reflecting the acute recovery reductions. These findings reflect the need for more consideration relative to the timing of instrument administration and the recovery experiences of members of this population. The true path of recovery may not be captured in its entirety if administrations do not occur in the months following CS+HIPEC. Without this information, patients' needs may remain unknown and unmet. Likewise, until recommendations are made relative to the appropriate timing of administrations, comparisons between datasets remain difficult.

Also making comparisons of findings across studies difficult is the use of numerous QOL instruments as well as the numerous variables that often are unreported or uncontrolled in the studies (McQuellon & Duckworth, 2009). In the located studies, various QOL instruments were utilized, including the FACT-C (colon) or FACT-G (general) (Cella et al., 1993), the SF-36, as well as both English and French versions of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (Aaronson, et al., 1993) and the QLQ-CR38 (colorectal module) (Sprangers, te Velde, & Aaronson, 1999). These instruments vary in terms of number of items, sensitivity, and question wording, complicating direct comparison between studies.

Additionally, alternate variables that likely impacted individuals' experiences and QOL reports, including social support, counseling assistance throughout the process, previous psychiatric history, and diagnosis often go unreported or are not controlled. Numerous primary diagnoses may result in peritoneal carcinomatosis, and individuals with differing primary diagnoses often are aggregated within these small samples. For

instance, of 67 potential study participants available to Schmidt et al. (2005), the following primary diagnoses were represented: appendix, ovary, colon, peritoneum, stomach, pancreas, liver, small bowel, retroperitoneal, sarcoma, uterus, and other. As the body of QOL research from these individuals is enhanced, more attention to some of the aforementioned variables and their impact on QOL data is needed.

It is apparent, then, that numerous limitations exist relative to the existing body of literature on long-term CS+HIPEC survivors. First, relatively few QOL studies of CS+HIPEC have been performed. Within these studies, numbers traditionally have been small, thereby limiting generalizations and reducing the power of statistical analyses. Likewise, by nature of the study designs, those who die or are experiencing the most significant symptomology often are not represented. Stringent inclusion and exclusion criteria in some studies limit potential participants to those who have no recurrent disease (e.g., Zenasni et al., 2009), further homogenizing the data to that provided by the healthier participants. Additionally, both instrument selection and the timing of instrument administration often vary, making across-study comparisons of results challenging. Finally, there is a dearth of phase III trials with individuals receiving CS+HIPEC. In the event that future national or international, multi-institutional trials are established, matched control groups could serve as true points of comparison relative to those receiving CS+HIPEC.

The current study will attempt to improve upon some of the existing limitations in previous QOL studies of survivors of CS+HIPEC. In attempt to acquire a more accurate and descriptive picture of the QOL and sleep quality of long-term survivors, the

investigator first located a large number of prospective participants. Undeniably, and similar to previous studies, those who did not live to be long-term survivors will not be represented in this study as well; yet alternate strategies will be implemented in order to acquire more representative data that depicts the range of current life conditions of those who have survived for 12 or more months post-CS+HIPEC. Specifically, the investigator will loosen study exclusion criteria, permitting all survivors (and not strictly those with no evidence of disease), to participate. Additionally, targeted strategies for avoiding missing data and achieving a high participation rate (i.e., personal phone calls and incentives) will be implemented. Utilizing these strategies, the researcher hopes to achieve not only more participants than did the investigators of past studies but also participants who represent a variety of potential outcomes. In addition to the inclusion of more participants and more diversity, larger numbers of participants will permit more complex analyses and the possibility of generalizing the findings. The use of a QOL instrument that has been utilized in previous studies also will facilitate the comparison of findings across studies. Finally, the addition of a measure assessing an under-studied construct, sleep quality, will serve to enhance this body of research by increasing awareness of an alternate life aspect potentially in need of additional attention.

Despite these improvements upon existing study designs, McQuellon et al. (2003) highlighted an obstacle confronted by QOL researchers when investigating long-term survivors.

“One vexing problem facing QOL researchers conducting long-term follow-up studies is to what extent a disease process and subsequent treatment have affected the patient’s

overall well-being compared with what changes in QOL would have occurred during the normal process of aging” (p. 161). An array of ancillary variables may be impacting the QOL and sleep quality of long-term survivors, and it is difficult to separate the effect of these ancillary variables from that of the procedure and disease process. Means of separating the impact of normal aging from that of the disease process and treatment do exist, however, and will be implemented in this study. First of all, the long-term QOL scores will be compared to standardized general population norms in order to acquire group comparisons. Secondly, (when available) the long-term QOL scores of survivors will be compared to personal baseline, pre-procedure scores to assess change within participants over time. These strategies should yield within-participant comparisons as well as comparisons between these survivors and members of the general population (McQuellon et al., 2003).

Conclusion

In conclusion, over the last few decades, CS+HIPEC has, over the last few decades, become a promising option for long-term survival in many patients with peritoneal carcinomatosis (al-Sammaa et al., 2008; Stewart et al., 2008) and may become even more so as surgeons continue to hone their skills, knowledge and selection criteria relative to the procedure. Simply because the invasive treatment has concluded for these individuals, however, their lives may be impacted by associated disease- and treatment-related variables. A biopsychosocial conceptual model, such as the Wilson and Cleary Model (1995), enhances researchers’ and clinicians’ understanding of how variables from differing domains may interact to impact the life quality of survivors. A need for more

methodologically sound studies with sufficient numbers of participants exists so that individuals can be truly informed decision makers pre-treatment and professionals remain informed of the QOL of these survivors. Ideally, such rich, descriptive psychosocial data can serve as the foundation of future interventions designed to improve survivors' QOL and sleep quality complications. In the realm of peritoneal carcinomatosis, considerations pertaining to quality must not be overshadowed by those pertaining to quantity.

CHAPTER III

METHODOLOGY

In Chapters I and II, the rationale and literature basis for the study of QOL and sleep quality in patients who received an aggressive treatment procedure were presented. The review of the literature demonstrated the dearth of current knowledge relative to the QOL and sleep quality of individuals who live at least 12 months following the CS+HIPEC. These findings support the need for additional psychosocial studies with these survivors. In this chapter, the methodology for conducting such a study is explained. Research questions and hypotheses are included. Also, participants and instrumentation are described, and data collection and statistical procedures are delineated.

Research Questions and Hypotheses

The aim of the present study was to acquire a better understanding of the QOL and sleep quality of cancer survivors who had CS+HIPEC a minimum of 12 months prior to the study date. Special attention was paid to both their mental and physical quality of life scores, how these scores compared to their own respective (baseline) scores prior to having the CS+HIPEC procedures (for the subset of patients on whom pre-surgery data was collected), and how their overall and component QOL scores compared to those of the general population. Sleep quality, a commonly reported concern and variable impacting QOL, also was examined among individuals in this population. Special attention was paid to the interrelations between sleep quality, quality of life, number of

months since procedure, and age at procedure. Finally, the contributions of selected surgical and physiological variables were examined in relation to their predictive power of QOL scores 12 (or more) months following CS+HIPEC in these survivors.

Research Question 1: What are the QOL subscale scores (i.e. Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health, Role Emotional) and component scores (i.e. Physical Component Score and Mental Component Score) of participants, as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) instrument, and how do they compare to those of general population norms?

Hypothesis 1a: The QOL subscale scores of participants will be lower than the standardized population norms.

Research Question 2: Regarding those participants for whom pre-surgical data is available, what differences exist between pre-surgical QOL subscale scores and 12 or more-month QOL scores for participants who received CS+HIPEC and have survived?

Hypothesis 2a: Post-surgical, 12-month Physical Functioning (PF), Role Physical (RP) and Bodily Pain (BP) subscale scores will be significantly higher than those acquired from Participants pre-surgery.

Research Question 3: What is the sleep quality of participants, as defined by one's global and component scores on the Pittsburgh Sleep Quality Index (PSQI)?

Hypothesis 3a: Global PSQI scores of the majority of CS+HIPEC patients will be above the recommended clinical threshold of eight, indicating poor sleep quality.

Research Question 4: What relationship exists between sleep quality, age at CS+HIPEC, months since surgery, and QOL subscale scores?

Hypothesis 4a: A significant positive relationship will exist between global sleep quality scores and the QOL subscale scores.

Research Question 5: What are the respective contributions of resection status (RO/R1, R2a, R2b, and R2c) and primary tumor site in predicting QOL subscale scores at 12 or more months?

Hypothesis 5a: Patients who achieved a better resection status will demonstrate higher QOL scores at 12 or more months.

Hypothesis 5b: Patients with appendiceal tumors and pseudomyxoma peritonei will demonstrate higher QOL scores at 12 or more months.

Participants

Participants were individuals who received CS+HIPEC at Wake Forest University Baptist Medical Center 12 or more months prior to the initiation of this study.

Participants' names were originally selected from a hospital database containing demographic information on all individuals who received CS+HIPEC at WFUBMC.

Participants' primary diagnoses varied, yet all had localized peritoneal carcinomatosis

that surgeons believed was amenable to complete resection and all were deemed sufficiently healthy to undergo this extensive procedure.

A subset of these individuals previously consented to participate in longitudinal QOL assessments via an alternate protocol prior to their hospital admission for CS+HIPEC. These individuals' pre-treatment QOL data also was available, therefore, for comparison purposes. The remaining participants were patients who had never been actively enrolled in a WFUBMC QOL study following CS+HIPEC, either because they were not offered the opportunity to participate in the ongoing assessments or were disinterested at the original time of consent.

All participants were English-speaking and had accurate contact information on file at the hospital. All participants provided both verbal and written consent prior to participating in this study. A summary of demographic characteristics of the sample is provided in Chapter 4.

Instrumentation

Participants completed two standardized instruments, a brief informational questionnaire, and a socio-demographic form. Instruments (Demographic Questionnaire, SF-36, PSQI and Patient Information Questionnaire) were randomly sequenced between participants in an effort to avoid differential impacts of fatigue on the concluding questionnaire(s). What follows is a description of the development and psychometric properties of the respective instruments.

Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)

Cognizant that an insufficient quantity of information on patients' disease and treatment experiences had been collected from the optimal sources (i.e., the patients themselves), a group of researchers developed the Medical Outcomes Study (MOS) in order to both gather this health-related information and examine the feasibility of utilizing self-administered, generic health surveys with populations with chronic medical and psychiatric conditions (Ware, Snow, Kosinski, & Gandek, 1993). The MOS surveys were based on a multidimensional model of health, including 40 mental and physical health concepts. This multidimensionality is integral in health assessments, as mental and physical conditions are not mutually exclusive. In fact, they often coexist in various severities in patient populations (McHorney et al., 1993).

Following the successful completion of the MOS, Ware and Sherbourne (1992) grew increasingly aware of the potential for participant burden in populations of the chronically ill and the associated costs of data collection with lengthy instruments. Ware and Sherbourne (1992) therefore desired to create a more feasible and practical instrument, without compromised psychometric characteristics or content coverage, for use in general population surveys, clinical practice and research, and health policy evaluation. Aware of the need to achieve standards of comprehensiveness across an array of health concepts yet concurrently keep patient burden considerations in mind, the developers attempted to balance depth and breadth considerations. In other words, they included in their measure the most frequently assessed concepts in existing

questionnaires and ensured they included a sufficient number of comprehensive items in order to measure each of the respective concepts accurately (Ware & Sherbourne, 1992).

The subsequent product, following previous versions (i.e., SF-18, SF-20), was the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; Ware et al., 1992), a self- or interviewer-administered (self administration will be used in this study), generic health survey yielding data that ultimately allows researchers to determine how individuals suffering from chronic medical or psychiatric conditions differ both from one another and the general population as a whole. Two versions of the SF-36 have been developed. Given that the subset of individuals who contributed baseline data (that will be analyzed for the purpose of assessing change over time in this study) completed version one of the SF-36, version one will be administered to all survivors in order to maintain this continuity between versions. The SF-36 is considered a “generic” health measure, as it assesses health concepts that are collectively valued. It is not disease, treatment or age-specific, but rather examines outcomes that are directly impacted by treatment and disease (Ware et al., 1993). It is precisely this “generic”, non-disease-specific, status that permits norm comparisons.

The SF-36 was designed for individuals age 14 or older and consists of one multi-item scale that measures eight health-related concepts (i.e. physical functioning (PF), role-physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH)) (Ware et al., 1993). McHorney, Ware, and Raczek (1993) noted it is insufficient to measure strictly mental and physical health in a comprehensive health assessment. Rather, information on the

limitations individuals experience as a consequence of their respective mental and physical health problems when attempting to engage in their usual life roles needs to be included as well. Role and social functioning scales were therefore included for this purpose (McHorney et al., 1993) as were additional operational definitions of the primary health concepts (i.e. functioning, well-being, disability and personal evaluation) throughout the scales (Ware et al., 1993).

For years, researchers examined the component structure of the SF-36 when used with the relatively healthy, general population and those with chronic conditions (Ware & Kosinski, 2001). If scales with the same component content are likely to lead to the same health conclusions, then researchers reasoned these scales are good candidates for aggregation (Ware & Kosinski, 2001). After repeated study, it became clear that the mental and physical components account for 80-85% of the reliable variance in the eight SF-36 scales across differing populations (Ware & Kosinski, 2001). Derived from the eight SF-36 scales, The Mental Component Summary (MCS) and Physical Component Summary (PCS) are the two comprehensive, distinct components measured in the survey. Researchers and practitioners can therefore examine the eight scales individually or the two component scores for scoring and interpretation purposes. The SF-36 measurement model is therefore predicated on three levels: 1) items; 2) scales that cluster these items; and 3) summary measures that aggregate the scales (MCS, PCS) (Ware & Kosinski, 2001). The eight subscales will comprise the unit of analysis for this study. A brief description of these eight scales follows.

Physical Functioning (PF) scale. Wanting to capture a range of physical limitations, the full, ten-item MOS Physical Functioning (PF) scale was incorporated into the short-form without adaptations (Ware et al., 1993). Participants are provided with an array of physical activities ranging from those vigorous in nature (e.g., participating in strenuous sports) to those less demanding (e.g., bathing or dressing oneself) and asked to rate the extent of limitation with each activity on a three-level continuum. The one self-care item included in this scale represents the “floor” of the scale (Ware et al., 2000). Those who achieve low scores on this scale are limited in performing all physical activities, from those mild to vigorous in nature, while those who achieve high scores are able to perform the range of physical activities without health-related limitations (Ware et al., 1993).

Role Emotional (RE) and Role Physical (RP) scales. The role functioning scales (RE ($n =$ three items), RP ($n =$ four items)) assess limitations in functioning due to emotional and physical problems, respectively. Specifically, these scales examine limitations in work or other typical activities, reductions in the amount of time spent in the aforementioned activities, and the difficulties experienced when performing these activities (Ware et al., 1993). A variety of roles are represented among the items, making the scales more responsive to those who have multiple roles. Low scores indicate substantial functional impairments in life roles due to mental and/or emotional problems (respectively), while higher scores indicate few role impairments due to mental or physical health-related problems. Response choices are dichotomized.

Bodily Pain (BP) scale. The BP questions ($n =$ two items) measure both the intensity of pain (on a six-point Likert scale) over the past four weeks as well as the level of interference with daily activities (on a five-point Likert-type scale). A low score indicates the individual experiences intense pain that interferes with daily activities, while a high score indicates minimal pain and minimal life interference due to pain (Ware et al., 1993).

General Health Perception (GH) scale. The GH scale is comprised of five questions that assess the participant's perception of her or his current health, health outlook and resistance to illness. Specifically, a single-item rating of health (i.e., poor to excellent) and four items from the Health Perceptions Questionnaire (Davies & Ware, 1981) were included (Ware et al., 2000). The inclusion of favorably and unfavorably worded items helps control for response set effects (Ware et al., 2000). This scale is also one of three dual-sided scales that yield a wider range of negative and positive health scores (Ware et al., 1993). In these scales, the absence of negative symptoms will not yield a high score. A respondent must report positive states or evaluate her or his respective health positively in order to receive a high score. A middle-range score is acquired when the respondent reports no symptoms or limitations but also no positive states (Ware et al., 1993).

Vitality (VT) scale. The VT scale consists of four items that measure the participant's energy and fatigue levels. The combination of favorably and unfavorably worded items is present in this scale as well. The VT scale is another of the three dual-sided scales (Ware et al., 1993). Low scores on the VT scale reveal the presence of

substantial energy deficits and fatigue; middle-range scores indicate minimal impairments or symptoms but no positive states or favorable ratings; high scores reveal minimal fatigue and high energy levels.

Social Functioning (SF) scale. The SF scale (n = two items) assesses both the extent and frequency with which physical or emotional problems have interfered with social activities. Low scores indicate physical or emotional problems have greatly interfered with social activities on a frequent basis, while high scores indicate the respondent has had minimal interruptions of typical social functioning due to physical or emotional problems.

Mental Health (MH) scale. The MH scale consists of five questions, one from each of the major mental health dimensions, including anxiety, depression, psychological well-being, loss of behavioral control and loss of emotional control (Ware et al., 1993). These five items are those that most accurately predict the 38-item summary score on the Mental Health Inventory (Ware et al., 1993). The MH is the last of the three dual-sided scales. Lower scores on the MH scale reveal the presence of problems in many of the major mental health dimensions; middle range scores reveal no mental health problems but no positive states or ratings either; high scores reveal the absence of psychological concerns and the presence of positive, healthy mental health states (Ware et al., 1993).

Reported Health Transition (RHT). Finally, the single reported health transition (RHT) question asks participants to rate the extent of change in their health over the past year. Although not included in the tabulated final score, the authors believe

this question yields useful information about individuals' perceptions of their health changes (Ware et al., 1993).

Various researchers have examined the psychometric properties of the SF-36, and numerous studies have provided evidence of instrument validity. Ware and Kosinski (2001) presented the correlations between the SF-36 scales and these principal Mental and Physical components in the MOS data ($n = 3,445$). As hypothesized, the PF (.88), RP (0.78) and BP (0.77) scales demonstrated the strongest correlations with the physical dimension, while the MH (0.12) and RE (0.19) scales were weakly correlated with the physical dimension. Alternately, the MH (.90), RE (.81) and SF (0.71) scales correlated most highly with the mental health component, while the PF (0.04), RP (0.30) and BP (0.24) scales correlated weakly with the mental health component. Of these scales, the MH and PF were the purest measures of the mental and physical health dimensions, respectively. McHorney et al. (1993) found similar results in their analyses and concluded that the interpretations of the MH and PF scales are unambiguous in their measure of clinical manifestations of mental and physical conditions, respectively (McHorney et al., 1993). The other mental and physical health scales measure alternate aspects of their respective dimension of health (Ware et al., 1993).

Not surprisingly, the three scales estimated to measure both the mental and physical health dimension (i.e., GH, VT, SF) demonstrated correlations with both dimensions of interest, making their interpretations more complex (Ware & Kosinski, 2001). Although correlated with both dimensions to some extent, some of these scales were more closely associated with one dimension over the other. For instance, the

researchers found that the GH scale was more strongly correlated with the physical dimension (0.68 vs. 0.32); the SF scale was more strongly associated with the mental health dimension (0.71 vs. 0.44); and the VT scale was virtually equally associated with both (0.57 vs. 0.59). Unlike the interpretation of the MH and PF scales, the interpretation of these three scales that measure components of both primary dimensions is more complex, and differences cannot be unequivocally related to one dimension or the other (McHorney et al., 1993). Their inclusion in the overall scale, however, remains vital so that clinicians and researchers can better understand the manifestations and impacts of both physical and mental health problems on daily functioning (McHorney et al., 1993).

In addition to the statistical validity, McHorney et al. (1993) also examined the clinical validity of the SF-36 scale in order to better understand its applicability and utility in a clinical setting. Specifically, the researchers examined the score profiles of four mutually exclusive adult patient groups (i.e. those with minor medical conditions, those with major medical conditions, those with solely psychiatric conditions and those co-morbid medical and psychiatric conditions) in order to examine the scale's ability to detect declines in health status associated with psychiatric and/or medical conditions. McHorney et al. (1993) found that the score profiles of SF-36 accurately differentiated between those with varying severities of medical and psychiatric conditions, suggesting strong clinical validity.

Also interested in the validity of the SF-36, McHorney, Ware, Lu, and Sherbourne (1994) examined the item discriminant validity. After completing 280 item-discriminant validity tests with 24 subgroups of individuals, they found that the correlations between

an item and its respective scale was higher than the correlation between the respective item and alternate scales 99.5% of the time. The correlations between each item and its respective scale exceeded correlations with all other scales by an excess of two errors 92.5% of the time (McHorney et al., 1994), suggesting strong item discriminant validity. Of the eight subscales, the GH scale demonstrated the most scaling variability across the diverse groups.

Researchers also have provided evidence for the reliability of the SF-36. McHorney et al. (1994) examined the reliability of the SF-36 across 24 patient subgroups differing in diagnoses, disease severity and sociodemographic characteristics. Internal-consistency reliability (Cronbach's alpha) for the combined sample ranged from 0.78 (GH) to 0.93 (PF). This lower reliability coefficient for GH can be attributed to the multidimensional nature of the items included to comprehensively assess the general health perceptions construct (McHorney et al., 1994). Some variability in internal-consistency reliability was noted across scales when administered to the 24 diverse subgroups (range: 0.65-0.94). Across all subscales among all tested subgroups, minimal Cronbach's alpha expectations were not met (i.e. 0.70) at solely one time point: the GH subscale for participants with comorbid psychiatric and complicated medical conditions. In fact, McHorney et al. (1994) reported that this group of patients with co-morbid psychiatric and complicated medical conditions had the lowest reliability estimates on three of the scales (GH, SF, and RP). For the remainder of the patient subgroups as well as the combined sample, minimal standards for internal-consistency reliability were met or exceeded.

In addition to validity and reliability considerations, McHorney et al. (1994) examined other characteristics of the data dispersion, including potential floor and ceiling effects. In a combined sample of diverse patient subgroups ($n = 3,445$), McHorney et al. (1994) noted that floor effects occurred less than 5% of the time in six of the eight scales but were fairly common in the RP and RE scales. Likewise, ceiling effects often occurred in the RP and RE scales as well as in the SF scale. They attributed these floor and ceiling findings in the role-scales to the fact that these are the “coarsest” of the eight scales, with only four (RE) and five (RP) levels each. Modest ceiling effects were also noted for the PF and BP scales (McHorney et al., 1994). Three of the SF-36 scales (i.e. GH, MH, and VT) are dual sided, balanced scales, meaning the absence of symptoms is insufficient to obtain a high score. To receive a high score on these scales, the respondent must endorse the absence of symptoms as well as the presence of positive symptoms. McHorney et al. (1994) found that these three dual-sided, balanced scales did not demonstrate floor and ceiling effects.

Finally, McHorney et al. (1994) examined the data completeness profiles across their 24 diverse subgroups. They noted a range of 75%-98% completeness, with a median completeness percentage of 91.5. Strictly the PF items had overall item-completeness rates of less than 80%, occurring predominantly among the sociodemographic groups that were most disadvantaged. Differences in item completeness were not better accounted for by subgroup membership. Rather, poverty, age and education were the best predictors, with those who were oldest, less educated and

more economically disadvantaged completing the least percentage of items (McHorney et al., 1994).

With the incorporation of norm-based scoring, results interpretation is relatively easy across subscales (Ware, n.d.). Specifically, linear transformations were used to transform scores on all scales (which had vastly different means when utilizing the 0-100 summative scoring) to a mean of 50 and a standard deviation of 10 (Ware, n.d.). The results from the general U.S. population census were utilized as the norm anchors, thereby adding an inherently meaningful anchor to each score (Ware, n.d.). For instance, any score below 50 is below that of the average person in the U.S., and every point below this norm of 50 signifies one-tenth of a standard deviation. With this basic knowledge, a reviewer of results can quickly gauge how many scores are below what would be expected in the general population. On the contrary, when utilizing the previous 0-100 summative scoring, a layperson would have no idea relative to the mean for each scale or how to deduce the relativity of scores on varying scales (Ware, n.d.). In conclusion, the use of norm-based scoring provides ease of results interpretation with the SF-36 scores.

Pittsburgh Sleep Quality Index (PSQI)

Designed by Buysse et al. (1989) for use with clinical populations, the Pittsburgh Sleep Quality Index (PSQI) is a client-rated instrument that assesses both sleep quality and sleep disturbances over the course of the four weeks prior to instrument administration. Although brief and simple, this instrument offers a comprehensive picture of one's sleep quality over the past month, making possible applications numerous. Among a plethora of additional uses noted by Buysse et al. (1989), the PSQI

facilitates clinicians' and researchers' identification of different groups of individuals within psychological and general medical settings, allows for a quick screening of sleep-wake disturbances and "good"/"poor" sleepers among patients, and assists in longitudinal research and clinical work by means of highlighting the course, nature and severity of sleep disturbances within and between populations over time.

During the early development stages of the PSQI, Buysse et al. (1989) agreed their specific aims included 1) creating a standardized measure of sleep quality that was both valid and reliable; 2) developing an instrument capable of differentiating poor from good sleepers; 3) introducing an instrument that was brief yet concurrently capable of detecting numerous sleep disturbances impacting one's quality of sleep; and 4) introducing an instrument that was both user-friendly and interpretable for clients, clinicians and researchers (Buysse et al., 1989). Three primary sources informed PSQI item derivation during this development period, including the authors' clinical experiences with patients struggling with impaired sleep quality, a literature review of existing sleep quality questionnaires, and the knowledge gained as a consequence of 18 months of field testing the instrument with various populations (Buysse et al., 1989).

During the 18-month field testing period, Buysse et al. (1989) administered the original items to three groups of individuals: controls ($n = 52$) without professed sleep-wake disturbances, "poor" sleepers diagnosed with Major Depressive Disorder (MDD; $n = 34$) and receiving outpatient or inpatient clinical interventions via the Western Psychiatric Institute and Clinic, and "poor" sleepers referred by their physicians to the Sleep Evaluation Center ($n = 62$) at the Western Psychiatric Institute and Clinic for a

myriad of sleeping and waking disturbances (Buysse, et al., 1989). All of the aforementioned 148 individuals completed the PSQI at least once, while a subgroup of 91 individuals (43 “good” sleepers, 22 individuals diagnosed with MDD and 26 individuals with sleep-wake disturbances) completed the PSQI a second time, an average of 28.2 days later (Buysse et al., 1989). By administering the PSQI to diverse populations, the authors were not only able to gain narrative feedback from diverse sources about their experiences while completing the instrument but were also able to compile global and component score profiles for each of the respective populations for comparison purposes.

The final version of the PSQI includes 24 items, 19 of which are client-rated and five of which are completed by either a bed partner or roommate, if applicable. The five items completed by a sleep observer are used strictly for clinical purposes and are not included in the scoring tabulation (Buysse et al., 1989). Instructions delineate the need for the participant to reflect upon her or his sleep quality over the past month. This targeted four-week time interval prior to instrument administration was intentionally selected by the authors in hopes of bypassing some of the concerns relative to alternate existing sleep measures (Buysse et al., 1989), noting that sleep instruments that broaden their focus to the previous year may not highlight the sleep concerns that are most pressing and pertinent to the current time. Conversely, sleep instruments that narrow the time frame of interest to strictly the previous night may not highlight themes and patterns of sleep disturbances relevant to the course of an individual’s sleep (Buysse et al., 1989). By targeting the past four weeks, the authors of the PSQI believe the instrument detects

currently relevant sleep-wake disturbances that have become more than transient problems.

For each of the 19 items, the scorer assigns an ordinal score, ultimately deriving a global PSQI score as well as seven component scores (i.e., sleep quality ($n =$ one item), sleep latency ($n =$ two items), sleep duration ($n =$ one item), habitual sleep efficiency ($n =$ four items), sleep disturbance ($n =$ eight items), use of sleeping medication ($n =$ one item) and daytime dysfunction ($n =$ two items)). Component scores, ranging from zero to three, are given equal value upon tabulation of the global PSQI score, indicating a possible global PSQI score of zero to 21 (Buysse et al., 1989). The global PSQI score will serve as the unit of analysis in the current study. Lower PSQI scores reflect better sleep quality, with a score of “zero” in a component score indicating no difficulty and a score of “three” reflecting severe difficulties. Buysse et al. (1989) established a global clinical cutoff score of five, meaning anyone scoring above this threshold is experiencing either severe problems in a minimum of two areas or moderate-intensity problems in more than areas. Scores, therefore, inherently reflect both the number and severity of sleep-wake disturbances (Buysse et al., 1989).

Various researchers have provided validity evidence for the PSQI. From a possible score range of zero to 21, scores derived from all three field-tested participant groups ranged from zero to 20. The global PSQI score was 2.67 +/- 1.70 for the “good” sleepers, 11.09 +/- 4.31 for those diagnosed with MDD, and 10.38 +/- 4.57 for those with a Disorder of Initiating and Maintaining Sleep (DIMS). The global scores for the diagnostic groups (MDD and DIMS) resembled one another yet differed significantly

from that of the controls (using sex and age as covariates in an ANCOVA). This similarity in profiles between those with MDD and DIMS makes sense, as individuals with depression typically have sleep initiation and maintenance disturbances similar to those with DIMS (Buysse et al., 1989). Based on these findings, the authors noted the existence of distinguishing global and component score profiles for the varying diagnostic groups (Buysse et al., 1989).

Beck, Schwartz, Towsley, Dudley, and Barsevick (2004) also reported support for the construct validity of the PSQI after finding statistically and clinically significant differences in the global sleep quality scores of heterogeneous groups of cancer patients with high and low fatigue, respectively. The validity of the instrument is further supported by the high rates of sensitivity (89.6%) and specificity (86.5%) maintained by the established cut-off score of five (Buysse et al., 1989). Together, these findings indicate the PSQI successfully differentiates the “poor” from the “good” sleepers and the individuals with varying diagnoses with characteristic sleep-wake disturbance features from controls.

Further evidence suggests that the PSQI may be valid for use with cancer survivors. Carpenter and Andrykowski (1998) examined the psychometrics of the PSQI with a heterogeneous group of cancer survivors, including bone marrow transplant survivors ($n = 155$), women with breast cancer ($n = 102$) at least three months following their primary treatment and women with benign breast problems ($n = 159$). Paying special attention to convergent and discriminant validity considerations, the authors examined correlations between global PSQI scores and other constructs. The correlations

between global PSQI scores and related constructs, such as sleep restlessness (as measured via the Center for Epidemiologic Studies-Depression), all exceeded 0.69, while correlations between global PSQI scores and unrelated constructs, such as nausea and vomiting, did not exceed 0.37 (Carpenter & Andrykowski, 1998), providing evidence of good convergent and discriminant validity.

Buysse et al. (1989) also examined the relationship between the PSQI and other measures of sleep quality. Specifically, Buysse, et al. (1989) examined the relationship between subjective PSQI scores and objective reports of sleep quality, as measured by polysomnography. With the exception of sleep latency, the authors found that PSQI scores did not correlate significantly with polysomnographic results. This finding is not surprising, however, given the differing time intervals of interest between the two tests (Buysse et al., 1989). While polysomnography provides a detailed, objective picture of the sleep quality of the participant's previous night's sleep, the PSQI instructions ask the participant to reflect upon his sleep quality over the course of the past four weeks. It is not unexpected, then, that these results are not significantly correlated to those from strictly the previous night's sleep. The objective polysomnographic results did, however, confirm group differences in the sleep quality of those belonging to the various field-tested groups (Buysse et al., 1989), thereby corroborating the PSQI findings that categorical differences exist in the sleep quality of controls versus those with MDD or DIMS.

Evidence for the reliability of the PSQI is also available. Buysse et al. (1989) reported a high degree of internal consistency among the seven component scores, with

an overall reliability coefficient (Cronbach's alpha) of 0.83 for the full scale, and concluded that the respective components are measuring a certain aspect of the same unifying construct (i.e., sleep quality), thus supporting the use of the full scale score. Carpenter and Andrykowski (1998) also calculated the Cronbach's alpha coefficient for the global PSQI scores and the 8-item sleep disturbances component scores of various groups of cancer survivors. These researchers reported that the Cronbach's alphas remained stable across participant groups for the global scores (0.80) and ranged from 0.70-0.78 for the sleep disturbances component scores. Additional authors (Beck et al., 2004) have corroborated the contributions of the seven component scores to the overall measurement of the sleep quality construct.

Test-retest reliability also was examined for the global and component scores of a subset of the field-tested participants ($n = 91$; $n = 43$ controls, 22 with MDD, 26 with sleep disorders) by means of paired t-tests and Pearson product-moment correlations (Buysse et al., 1989). Participants were administered the second instrument a mean of 28.2 days following the initial administration. Paired t-tests for the combined global and component scores showed no significant differences between T1 and T2, suggesting stability in scores across time. The Pearson product moment correlations also demonstrated the reliability in scores across time for the combined group. The T1-T2 correlation coefficient for the entire group was 0.85 ($p < 0.001$), while component scores ranged from 0.84 (sleep latency) to 0.65 (medication use), with variability in patterns and amounts medicine use not expected. When examining the various patient groups, Buysse et al. (1989) noted that the scores of the patients with MDD demonstrated two significant

differences across the two administrations: a reduction in sleep disturbances and reduced daytime dysfunction (changes which may be accounted for by exterior factors).

Although demonstrating more variability, both the global and component scores within the respective subgroups were significantly correlated across the two administrations, with the sole exception being the medication use subscale (Buysse et al., 1989). Overall, test-retest reliability estimates are strong.

In addition to validity and reliability considerations, researchers have examined additional PSQI-related issues in the cancer care arena, including the frequency of missing data. Missing data among self-administered PSQI instruments is especially worrisome, as missing items can cumulatively result in missing component scores and ultimately missing global PSQI scores (Beck et al., 2004). Cognizant of the high levels of fatigue and additional co-morbid symptoms in cancer patients and survivors, Carpenter and Andrykowski (1998) examined the PSQI instruments completed by a heterogeneous group of cancer survivors for missing data. Upon analysis of the frequency distributions, the authors found <4% of the individual item data was missing for the cancer survivor responders. The items most commonly left incomplete included those seeking information as to the reason behind the troubled sleep on the sleep disturbances component of the instrument (Carpenter & Andrykowski, 1998). The authors extrapolated that individuals who leave these items blank may experience disturbed sleep for alternate reasons not adequately represented and suggested clinical follow-up interviews may successfully reduce this problem further.

Beck et al. (2004) reported a much higher preponderance of missing data among their participants, with an inability to calculate 21% of their first study participants' global PSQI scores. These authors found higher rates of missing data for the "usual bed time" questions. Instead of providing a numerical time, many participants provided a "yes/no" answer, ultimately preventing the researchers from calculating the sleep efficiency component score and therefore the global sleep quality score as well. Enhancing their second study with a follow-up phone call in the event of missing data, Beck et al. (2004) managed to reduce this percentage from 21% to 4.2%.

Buysse et al. (1989), Carpenter and Andrykowski (1998) and Beck et al. (2004), all concluded the psychometric characteristics of the PSQI are strong. Beck et al. (2004) encouraged its continued use with cancer patients exhibiting a wider range of both racial and ethnic characteristics. Disagreement remains between the developers of the instrument and Carpenter and Andrykowski (1998) as to the optimal clinical cut-off score for those with significant sleep-wake disturbances. While Buysse et al. (1989) maintain five is the optimal cut-off score for a "case", Carpenter and Andrykowski (1998) found the mean PSQI scores were greater than eight (rather than five) in all groups with sleep problems. They recommended using eight, rather than five, as a clinical cut-off score with cancer patients to signify the presence of poor sleep quality and reduce the possibility of false positives. The original instrument developers continue to suggest the use of five as a clinical cutoff score. Because of this discrepancy in the literature as to what constitutes a clinical cutoff, the more conservative cutoff of eight will be used.

Patient Information Questionnaire

A description of the full Patient Information Questionnaire given to participants is beyond the scope of this dissertation, as much of the data collected on this instrument will be analyzed for research being conducted by faculty at the hospital at which the study is being conducted. Essentially, this questionnaire contains a total of 19 questions that represent the collective suggestions of the primary mental health practitioners and surgical oncologists who work with this population at this hospital. The contributors felt that the topics addressed by these questions (a mixture of Likert-type, dichotomized, and open-ended response formats) are insufficiently covered in the included questionnaires yet very important to the holistic care of this population. They were therefore included for the purpose of enhancing the team's understanding of the population's recovery post-treatment. The findings associated with these questions could potentially lead to subsequent research investigations but the majority were not analyzed as part of this dissertation.

For the purposes of this study, only responses to question number two (*My sleep quality prior to surgery + heated chemotherapy (IPHC) was poor*) were examined. Respondents answered on a five-point Likert-type scale that ranges from “not at all” to “very much”. This question was added because the selected sleep quality questionnaire (PSQI; Buysse et al., 1989) strictly assesses sleep quality over a four-week period following CS+HIPEC. Without this research question, the researcher has no way of knowing who struggled with poor sleep quality prior to the procedure (i.e., who has chronic sleep quality problems).

Demographic Questionnaire

Participants completed a Demographic Questionnaire containing questions about the following information: name, gender, address, phone number, age, date of birth, diagnosis, date of diagnosis, physician, race, ethnicity, marital status, housemates, annual salary, highest grade in school completed, current employment status, occupation, partner's occupation, type of insurance, any active medical treatments, date of most recent treatment, and most troubling symptoms.

Procedures

Prior to its development, the prospective study was discussed with behavioral researchers as well as surgical oncologists who routinely work with and study patients who receive CS+HIPEC at WFUBMC. The team decided to expand the study, making this dissertation a component of a larger study. In addition to the instruments described above, two additional instruments were included: the Functional Assessment of Cancer Therapy Colorectal (FACT-C) (Ward et al., 1999) and the FACIT Treatment Satisfaction scale (FACIT-TS) (Hahn et al., 2000).

After gaining permission from the Hospital Institutional Review Board (IRB) to proceed with data collection, potential participants' names were located in the hospital database containing the demographic and surgical information of all of the individuals who have received CS+HIPEC at WFUBMC. The names of all individuals who received treatment 12 months prior to the initiation of the study were retrieved.

Next, a telephone script pre-approved by the hospital IRB was used to make contact phone calls to potential participants. The purpose of the telephone call was to

explain the purpose of the study and receive verbal consent from the prospective participant to mail: 1) a cover letter detailing the study, 2) a formal written consent, and 3) a battery of instruments to her or his address. Two researchers, including the primary investigator of this dissertation and a post-doctoral member of the hospital CS+HIPEC research team, conducted the telephone calls over a two week period. Three rounds of calls were completed, with messages and return phone numbers left only once. The utilization of telephone scripts permitted relative uniformity during these calls.

Two slightly different versions of the phone script were created, one for individuals who previously opted to participate in the existing CS+HIPEC QOL study and the other for the individuals who have not participated in a CS+HIPEC-related QOL study at WFUBMC. The script for previous participants differed from the other version only in that it thanked them for their previous contributions and delved into slightly less depth about the nature of QOL studies. All participants were told that the researchers are interested in acquiring information about the quality of life and sleep quality of individuals living one or more years post-treatment. Prospective participants were told that their contributions will inform the team's comprehensive understanding of and future work with this population. Additionally, they were given instructions related to completion of the consent form and how to contact the principal researcher, informed of the approximated completion time, and offered a \$25 gas card, provided by the hospital, as a token of appreciation for their contributions. Individuals were told that they would be mailed the gas card along with their copy of the signed consent form upon receipt of their completed instruments. They also were informed of the possibility of receiving a

follow-up phone call if: a) they neglected to return the packet, b) missing data was evident, or c) the researcher was interested in inquiring further about certain responses.

The individuals who verbally agreed to the mailing were mailed a packet containing a brief cover letter, written consent form, the instrument packet and a self-addressed, postage-stamped return envelope for their convenience. The consent form included a statement regarding the possibility of researchers making follow-up phone calls with the participants. While not explained further to participants, the researcher introduced this possibility in the event of missing data or the presence of clinically alarming QOL scores, as defined by two or more standard deviations below the population norms.

Upon receipt of returned packets, the primary researcher examined the packet for completeness. If complete, the data was entered into the established database, and both the gas card and a copy of the signed consent form were mailed to that respective individual. If incomplete, a follow-up phone call was performed to retrieve any missing data. Occasionally, blank instruments, or single pages within instruments, were returned in hopes of obtaining complete datasets from participants. Individuals who did not return packets were called approximately two weeks from the day of the initial mailing. Numerous participants neglected to return the written consent form with their data, requiring the primary investigator to resend the consent form and a return envelope. If no consent form was received, the data were lost.

The data was compiled and scored as it was received. Statistical analyses were performed when data retrieval and scoring were complete.

Data Analysis

Each research question yielded information about this respective group of surgical oncology patients. Descriptive statistics of demographic information were calculated in order to provide a profile of the sample. Additionally, estimates of internal consistency (Cronbach's alpha) were calculated for all study variables. Descriptive statistics also were calculated for the component and subscale QOL scores of participants, and z-statistics were calculated by comparing these sample scores with population parameters. A subset of the sample has both pre-surgical QOL data on file as well as the data acquired in the current cross-sectional study. For this subset of the sample, paired t-tests with all eight subscale scores and the two component scores were performed to assess whether significant change occurred between the pre-surgery and 12 or more month QOL scores. Additionally, the respective contributions of resection status and primary tumor site to 12 or more month QOL scores were examined with two separate two-way ANOVAs. Through a t-test, the means of these primary tumor site groups were compared as well. Descriptive statistics also were utilized to better understand the global and component sleep quality scores of participants. A t-test also was performed in order to examine whether the mean sleep quality scores of this sample significantly differed from scores of other cancer populations that were used in order to determine the recommended clinical cutoff score. Finally, Pearson correlation coefficients demonstrated the magnitude of relationships between each of the QOL subscale and component scores, the global PSQI scores, age at CS+HIPEC, and months since procedure.

Table 1

Research Questions, Hypotheses, Variables, and Analyses

<u>Research Question 1:</u> What are the QOL subscale scores (i.e. Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health, Role Emotional) and component scores (i.e. Physical Component Score and Mental Component Score) of participants, as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) instrument, and how do they compare to those of general population norms?		
<u>Hypothesis</u>	<u>Variables</u>	<u>Analysis</u>
<i>Hypothesis 1a: The QOL subscale scores of Participants will be lower than the standardized population norms.</i>	-PF, RP, RE, BP, GH, VT, SF, and MH subscale scores (continuous) -Component QOL scores (continuous) -Standardized population norms for the QOL component & subscale (n=10) scores (continuous)	Descriptive statistics z-statistics
<u>Research Question 2:</u> Regarding those participants for whom pre-surgical data is available, do differences exist between pre-surgical QOL subscale scores and 12 or more-month QOL scores for participants who received CS+HIPEC and have survived?		
<u>Hypothesis</u>	<u>Variables</u>	<u>Analysis</u>
<i>Hypothesis 2a: Post-surgical, 12-month Physical Functioning (PF), Role Physical (RP) and Bodily Pain (BP) subscale scores will be significantly higher than those acquired from Participants pre-surgery.</i>	-Pre-surgical QOL subscale and component scores (n=10) (continuous) -Post-surgical QOL subscale scores and component scores (n=10) (continuous)	Paired t-tests
<u>Research Question 3:</u> What is the sleep quality of participants, as defined by one's global and component scores on the Pittsburgh Sleep Quality Index (PSQI)?		
<u>Hypothesis</u>	<u>Variables</u>	<u>Analysis</u>
<i>Hypothesis 3a: Global PSQI scores of the majority of CS+HIPEC patients will be above the recommended clinical threshold of 8, indicating poor sleep quality.</i>	-global PSQI score (continuous) -component scores (n=7): sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, daytime dysfunction (continuous)	Descriptive statistics t-test

<u>Research Question 4:</u> What relationship exists between sleep quality, age at CS+HIPEC, months since surgery, and QOL subscale scores?		
<u>Hypothesis</u>	<u>Variables</u>	<u>Analysis</u>
<i>Hypothesis 4a: A significant positive relationship will exist between global sleep quality scores and the QOL subscale scores.</i>	Post-surgical, 12-month QOL subscale and component scores (n=10) (continuous) -global PSQI score (continuous) -age at CS+HIPEC (continuous) -months since procedure (continuous)	Correlation Matrix
<u>Research Question 5:</u> What are the respective contributions of resection status (RO/R1, R2a, R2b, and R2c) and primary tumor site in predicting QOL subscale scores at 12 or more months?		
<u>Hypothesis</u>	<u>Variables</u>	<u>Analysis</u>
<i>Hypothesis 5a: Patients who achieved a better resection status will demonstrate higher QOL scores at 12 or more months.</i> <i>Hypothesis 5b: Patients with appendiceal tumors and pseudomyxoma peritonei will demonstrate higher QOL scores at 12 or more months.</i>	-Primary tumor site (categorical data) -Resection status (categorical, independent variable) -Component QOL scores (continuous; dependent variable)	Two-way ANOVAs t-test

Pilot Study

A pilot study was conducted to field test the instrumentation and instructions, to gauge the time requirements relative to the verbal consent phone calls and the data collection process, and to acquire estimations of both the projected response rate for the full study and the percentage of survivors in the existing database for whom phone contact was not possible. The main purpose of the pilot study, then, was to assess the

ease of participant recruitment and uncover any procedural adjustments that needed to be made to fortify the full study. Detailed pilot study methodology and results are provided in Appendix C. An overview of what was gleaned from pilot study participants and how this information has been incorporated into the full study follows.

When conversing with prospective participants over the phone in order to obtain their verbal consent to mail the packet of instruments to their home address, patients were invited to share any feedback related to the length of time needed to complete the packet and any items that appeared confusing. Additionally, participant packets were analyzed to assess for any apparent trends in terms of missing, incomplete, or misunderstood items. Some of this direct and indirect feedback has been incorporated, while other feedback was not. What follows is a summary of the direct and indirect feedback and the rationale for its inclusion or exclusion, respectively.

Feedback

All individuals who completed the instruments followed the written instructions provided with the mailed packet. Specifically, they signed and dated the written consent and returned it along with their completed packets. Additionally, all but one prospective pilot participant returned the contents in a one-week period from their reception of the packet. During the initial phone contact, patients were asked to indicate on the packet if it took an excess of 20 minutes to complete the pilot instruments. No one made any indications suggesting the completion time exceeded this specified time frame. One prospective pilot participant did, however, call the investigator to state that the completion of the battery in its entirety was too much given her current state of health.

Rather than complete, or partially complete, select instruments, the prospective participant returned the entire battery without any data. This incident suggests that those who are experiencing significant health complications may find the idea of completing a battery of instruments requiring approximately 20 minutes of time to be a daunting endeavor. Consequently, if prospective participants indicated such concerns over the initial verbal consent phone call in the full study, they were given the non-pressured option of completing select instruments, as their health and mindset allowed, so that it was possible to acquire *some* data from any individuals with similar concerns.

Other indirect feedback was obtained while reviewing the returned instruments. Given the importance of obtaining participants' primary diagnosis for certain analyses, the accuracy of this diagnostic information that they were asked to provide on the sociodemographic form is essential. While some participants provided accurate primary diagnoses, others simply indicated they had peritoneal dissemination. For the purposes of accuracy and consistency, the primary diagnosis of each participant was pulled from the existing CS+HIPEC database of WFUBMC for the full study.

Additionally, in numerous instances, participants selected more than one response choice on the SF-36 and PSQI items. Although scoring strategies are in place for such occurrences, the cleanest conclusions can be drawn from analyses of the one best response provided by the respective participants. On the PSQI, these numerous responses often took the form of a *range* of bed times, waking times, or typical hours of sleep. In an attempt to acquire the most suitable or representative response for each question in the full study, interested prospective participants were asked in the initial phone contact to

select or offer the *one* response choice that was most representative or typical for each item.

Finally, the completion of all of the requisite steps of the pilot study informed the investigator's understanding of the procedural aspects of the study. First, the estimated time allocation for each of the initial telephone contacts in order to obtain verbal consent for the mailing was insufficient. In general, patients appreciated the phone contact and often took the opportunity to update the investigator on her or his health status, QOL, and upcoming appointments, thereby lengthening the estimated call duration. Additionally, many patients requested certain hospital triage numbers in order to reach someone who could answer their medical questions or check appointment dates. These numbers were acquired and available when additional questions arose in the full study. Finally, of the prospective pilot participants who were randomly pulled from the database, those who were contacted were more frequently retired and not working or disabled. This is likely because the phone calls predominantly occurred during normal business hours. Messages were left on many answering machines, and numerous working individuals returned the message expressing interest in participating in the study. In addition to having some form of voicemail, these working individuals who returned the calls demonstrated some initiative on their parts. Together, these findings related to the results of the initial verbal consent pilot phone calls suggested that the time allocated for each phone call needed to be increased, appropriate telephone triage numbers of WFUBMC needed to be on hand, and phone call times needed to be extended to after hours in order to target working individuals.

Summary

Additional descriptive information is needed on the survivors of CS+HIPEC. In this study, the researcher examined the quality of life and sleep quality of these survivors and investigated the role of certain demographic and clinical variables in predicting long-term QOL within these individuals. In this chapter, the research questions and hypotheses were outlined, a description of participant recruitment was provided, the instrumentation and procedures were expressed, and the intended data analyses were offered. Lastly, direct and indirect feedback obtained via the pilot study was described, and changes implemented to enhance the integrity of the full study were listed.

CHAPTER IV

RESULTS

In this chapter, the results of the study are presented by means of both descriptive and inferential statistics. First, the sample characteristics are described. Next, the psychometric characteristics of the instruments are reported. Finally, the results of the analyses performed to test the respective hypotheses are described.

Sample Characteristics

Following a database search for all WFUBMC patients living 12 or more months post CS+HIPEC, 205 individuals were located in addition to the 17 who were invited to participate in the pilot study. Of these prospective 205 individuals, the investigator learned that two individuals died during the phone call time frame, leaving 203 potential participants. Of these 203 remaining individuals, 35 persons had numbers that were disconnected or inaccurate. Removing those who did not have accurate contact information, the investigator counted a total of 168 potential participants. At the conclusion of the calling period, 124 of the 168 individuals had given verbal consent for the mailing and only two individuals declined participation. The remaining 42 qualifying individuals were not reached via telephone and did not return the voice messages. Of note, the investigator learned, through loved ones and caregivers, that some of these 42 individuals with whom she did not converse directly were sick, in hospitals with complications, or at home with hospice care. Of the 124 individuals who gave verbal

consent to the mailing, 63 participated previously in a longitudinal research study in which they provided baseline, pre-surgical QOL information. The other 61 individuals did not participate and therefore did not have baseline data available for comparison purposes.

The final sample consisted of 82 CS+HIPEC survivors (55.56% female ($n = 45$) and 44.44% male ($n = 36$)) ranging from 13 months to 180.2 months post-procedure ($m = 48.9$ months, $sd = 39.6$ months). This number reflects a 49% overall response rate (i.e. 82/168) and a 66% response rate from those who gave verbal consent for the mailing (i.e. 82/124). Age at the time of study completion ranged from 23 to 87 ($m = 58.4$, $sd = 12.4$), while age at CS+HIPEC ranged from 21 to 80.0 ($m = 54.9$, $sd = 11.8$). Relative to race, 79.27% of the sample self-identified as White ($n = 65$), 12.20% as Black ($n = 10$), 4.88% as both White and Native American ($n = 4$), 2.44% as Asian ($n = 2$), and 1.22% as Native American ($n = 1$). All but 1.25% of the sample self-identified as Non-Hispanic. Post-surgery, 60% ($n = 48$) were classified as receiving a R0/R1 resection status, 30% ($n = 24$) were classified as receiving an R2a resection status, and 10% ($n = 8$) received an R2b resection status. Finally, primary tumor sites most commonly represented among final sample participants included appendix (60.49% ($n = 49$)), colon (14.81% ($n = 12$)), ovary (7.41% ($n = 6$)), and mesothelioma (6.17% ($n = 5$)), among others. For these, and other, descriptive statistics, please refer to Tables 2-8.

Table 2

Descriptive Statistics: Current Age, Age at CS+HIPEC, Months since Surgery

Variable	Mean	Std Dev.	Median	Minimum	Maximum
Age (current)	58.4	12.4	61.0	23.0	87.0
HIPEC age	54.9	11.8	56.0	21.0	80.0
Time_since_surgery (mo.)	48.9	39.6	33.9	13.0	180.2

Table 3

Descriptive Statistics: Resection Status

Resection Status	Frequency	Percent	Cumulative Frequency	Cumulative Percent
R0/R1	48	60	48	60.00
R2a	24	30	72	90.00
R2b	8	10	80	100.00

Note: Frequency Missing = 2

Table 4

Descriptive Statistics: Gender

Gender	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Female	45	55.56	45	55.56
Male	36	44.44	81	100.00

Note: Frequency Missing = 1

Table 5

Descriptive Statistics: Ethnicity

Ethnicity	Frequency	Percent	Cumulative Frequency	Cumulative Percent
H	1	1.25	1	1.25
NH	79	98.75	80	100.00

Note: Frequency Missing = 2

Table 6

Descriptive Statistics: Race

Race	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Asian	2	2.44	2	2.44
Black	10	12.20	12	14.63
Native American	1	1.22	13	15.85
White	65	79.27	78	95.12
White & Native American	4	4.88	82	100.00

Table 7

Descriptive Statistics: Primary Cancer Site

Site	Frequency	Percent	Cumulative Frequency	Cumulative Percent
GIST	2	2.47	2	2.47
PMP-disseminated peritoneal mucinous	1	1.23	3	3.70
Appendix	49	60.49	52	64.20
Appendix & colon	1	1.23	53	65.43
Appendix; DPAM	1	1.23	54	66.67
Colon	12	14.81	66	81.48
Mesothelioma	5	6.17	71	87.65
Ovary	6	7.41	77	95.06
Rectal	2	2.47	79	97.53
Sarcoma	1	1.23	80	98.77
unknown	1	1.23	81	100.00

**Frequency Missing = 1*

Note: GIST= Gastrointestinal Stromal Tumor; PMP= Pseudomyxoma Peritonei; DPAM= Disseminated Peritoneal Adenomucinous

Table 8

Descriptive Statistics: Marital Status

Marital Status	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Single	5	6.10	5	6.10
Married	57	69.51	62	75.61
Separated	2	2.44	64	78.05
Divorced	9	10.98	73	89.02
Widowed	9	10.98	82	100.00

Instrument Psychometrics

Within the SF-36 subscales, measures of internal consistency ranged from 0.76 (MH) to 0.93 (PF) with a median alpha of .85, while the Cronbach's alpha estimate for the global PSQI measure was 0.75. These estimates of internal consistency support the reliability of these measures with this sample (see Table 9).

Table: 9
Internal Consistency of Measures

Measure	Cronbach's Alpha
SF36: PF	0.932
SF36: RP	0.907
SF36: BP	0.875
SF36: GH	0.820
SF36: VT	0.870
SF36: SF	0.830
SF36: RE	0.815
SF36: MH	0.758
PSQI Global	0.753

Note: PF = Physical Functioning; RP = Role Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; PSQI = Pittsburgh Sleep Quality Index

Hypothesis Testing

The results of analyses to test the following research questions are delineated below.

1. What are the QOL subscale scores (i.e. Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health, Role Emotional) and component scores (i.e. Physical Component Score and Mental Component Score) of participants, as measured by the Medical Outcomes Study 36-Item Short-Form Health

Survey (SF-36) instrument, and how do they compare to those of general population norms?

2. Regarding those participants for whom pre-surgical data is available, what differences exist between pre-surgical QOL subscale scores and 12 or more-month QOL scores for participants who received CS+HIPEC and have survived?

3. What is the sleep quality of participants, as defined by one's global and component scores on the Pittsburgh Sleep Quality Index (PSQI)?

4. What relationship exists between sleep quality, age at CS+HIPEC, months since surgery, and QOL subscale scores?

5. What are the respective contributions of resection status (RO/R1, R2a, R2b, and R2c) and primary tumor site in predicting QOL subscale scores at 12 or more months?

Research Question 1

Research question one pertained to the QOL scores of CS+HIPEC survivors. In Tables 10-11, the QOL means, standard deviations, confidence intervals, and z-statistics are delineated for the subscale and component scores. Figure 2 offers a graphical display of the QOL mean scores.

Table 10

Quality of Life: Norm-based Scores and Confidence Intervals for Mean Scores

Variable	N	Mean	Std. Dev.	Median	25 th Pctl	75 th Pctl	Minimum	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
PF_NBS	82	45.9	11.1	49.8	38.3	55.1	15.2	57.1	43.5	48.3
RP_NBS	81	46.9	11.7	56.2	35.0	56.2	28.0	56.2	44.3	49.5
BP_NBS	82	52.7	10.3	55.9	42.2	62.8	28.9	62.8	50.4	54.9
GH_NBS	82	49.4	10.2	50.9	43.9	57.0	24.2	64.0	47.2	51.7
VT_NBS	82	52.4	10.4	53.8	44.3	60.9	23.0	70.4	50.1	54.7
SF_NBS	82	51.1	9.3	57.1	46.3	57.1	13.7	57.1	49.1	53.2
RE_NBS	82	49.9	10.2	55.3	44.8	55.3	23.7	55.3	47.7	52.2
MH_NBS	82	54.0	8.2	57.3	50.4	59.5	32.3	64.1	52.2	55.8
PCS	82	47.0	10.7	51.2	37.2	55.5	19.8	60.3	44.6	49.3
MCS	82	53.9	8.3	56.0	50.8	59.2	25.9	68.9	52.1	55.7

Note: PF_NBS = Physical Functioning Norm-based Score; RP_NBS = Role Physical Norm-based Score; BP_NBS = Bodily Pain Norm-based Score; GH_NBS = General Health Norm-based Score; VT_NBS = Vitality Norm-based Score; SF_NBS = Social Functioning Norm-based Score; RE_NBS = Role Emotional Norm-based Score; MH_NBS = Mental Health Norm-based Score; PCS = Physical Component Score; MCS = Mental Component Score

The norm-based QOL scores, standard deviations, and ranges are listed for each scale and component score. First, percentiles and 95% confidence intervals were established around the observed mean scores in order to demonstrate score ranges. If a confidence interval did not include 50 (i.e. the norm-based mean), it was possible to gauge, at an alpha level of 0.05, if a respective mean was either lower or higher than that of the standardization sample. In Table 11, z-statistics that were calculated with general population parameters are displayed. The scores that differed significantly from 50 at the .05 level are bolded. Because there were a large number of analyses being conducted, Bonferroni corrections were used to control Type I error, and a more conservative

significance level of $p = 0.005$ was used. In Table 11, those scores that differed significantly from 50 at the $p = 0.005$ level are marked with an asterisk.

Figure 2: Norm-based QOL Subscale and Component Scores

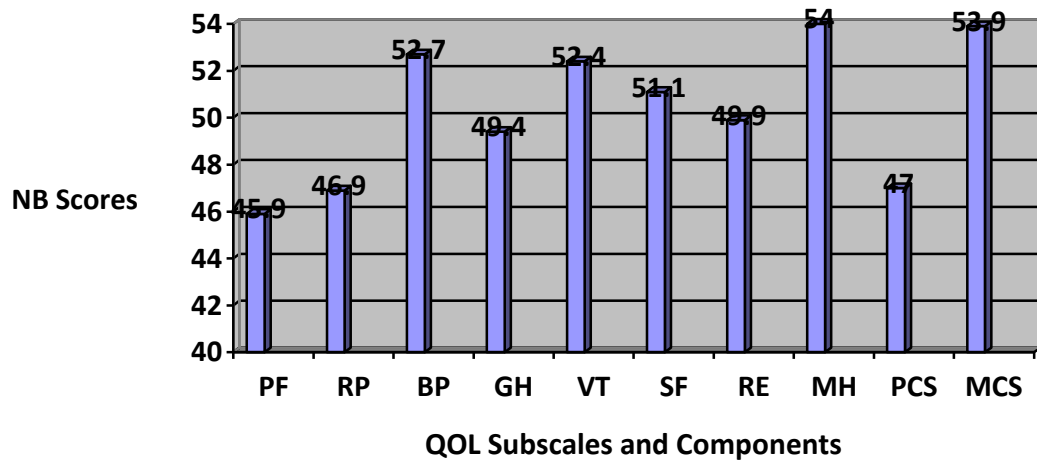


Table: 11
Quality of Life: z-statistics and p-values

Scale	z-statistic	p-value
PF*	-3.373	<0.001
RP	-2.354	0.019
BP	2.352	0.019
GH	-0.497	0.619
VT	2.086	0.037
SF	1.085	0.278
RE	-0.049	0.961
MH*	4.422	<0.001
PCS	-2.540	0.011
MCS*	4.228	<0.001

Note: PF = Physical Functioning; RP = Role Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; PCS = Physical Component Score; MCS = Mental Component Score

Contrary to what was hypothesized, all QOL scores of participants were not significantly lower than the population norms. Rather, in this sample, the PF ($z = -3.373$, $p = < 0.001$) scores were significantly lower than those of the general population, while the MH ($z = 4.422$, $p < 0.001$) scores and the MCS ($z = 4.228$, $p = < 0.001$) were significantly higher than those of the general population.

Although the Bonferroni correction $p = 0.005$ was utilized to determine the actual significance of the scores, it is important to take note of those scores that were not significant at the $p = 0.005$ level yet differed from the population parameters at the $p = 0.05$ level. Scores with p values less than 0.05 but greater than 0.005 included those associated with the RP ($z = -2.354$, $p = 0.019$) scale and PCS ($z = -2.540$, $p = 0.011$), as well as the BP ($z = 2.352$, $p = 0.019$) and VT ($z = 2.086$, $p = 0.037$) scores. Utilizing this conservative cut point, these scores were not considered significantly different from the population means, unlike the Physical Functioning, Mental Health, and Mental Component scores. If a less conservative test of significance was utilized or if a larger sample was attained, however, it is possible that these scores would be considered significantly different from the population norms as well.

In conclusion, one is able to conclude from these scores that these survivors continue to fare significantly worse than their general population counterparts in a physical capacity. Their mental health, however, was significantly better. The hypothesis that all QOL scores would be lower than those of the population norms was not supported.

Research Question 2

The purpose of research question two was to examine the significance of changes between baseline and follow-up QOL scores in each of the mean scale and component scores. Each person served as a control for her- or himself, and alpha levels were adjusted prior to the analyses. The results of these analyses are reported below (see Tables 12-21) for the 41 participants for whom baseline data were available. Again, a Bonferroni correction ($p = 0.005$) was utilized to determine the actual significance of the scores. For reference, those scores that were not significant at the $p = 0.005$ level yet differed at the $p = 0.05$ level are bolded as well. In Figure 3, a graphical display of these changes is depicted.

Table: 12

Paired t-test: Change at Follow-up, Physical Functioning

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
PF_NBS_BL	41	47.5	9.3	48.8	19.4	57.1	
PF_NBS	41	47.7	10.1	50.9	23.6	57.1	
PF change	41	.2					0.8857

PF_NBS_BL: Physical Functioning Norm-based Score Baseline; PF_NBS: Physical Functioning-Norm-based Score

Table: 13

Paired t-test: Change at Follow-up, Role Physical

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
RP_NBS_BL	41	44.9	12.8	56.2	28.0	56.2	
RP_NBS	41	48.1	10.9	56.2	28.0	56.2	
RP change	41	3.3					0.183

RP_NBS_BL: Role Physical Norm-based Score Baseline; RP_NBS: Role Physical-Norm-based Score

Table: 14

Paired t-test: Change at Follow-up, Bodily Pain

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
BP_NBS_BL	41	52.8	10.0	55.9	33.2	62.8	
BP_NBS	41	53.7	9.9	55.9	37.5	62.8	
BP change	41	0.9					0.616

BP_NBS_BL: Bodily Pain Norm-based Score Baseline; BP_NBS: Bodily Pain-Norm-based Score

Table: 15

Paired t-test: Change at Follow-up, General Health

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
GH_NBS_BL	41	49.8	7.5	50.9	31.2	64.0	
GH_NBS	41	51.1	8.8	50.9	31.8	64.0	
GH change	41	1.3					0.337

GH_NBS_BL: General Health Norm-based Score Baseline; GH_NBS: General Health Norm-based Score

Table: 16

Paired t-test: Change at Follow-up, Vitality

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
VT_NBS_BL	41	52.4	9.3	53.8	25.4	70.4	
VT_NBS	41	54.0	8.9	56.2	37.2	70.4	
VT change	41	1.6					0.366

VT_NBS_BL: Vitality Norm-based Score Baseline; VT_NBS: Vitality Norm-based Score

Table: 17

Paired t-test: Change at Follow-up, Social Functioning

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
SF_NBS_BL	41	47.5	10.4	46.3	13.7	57.1	
SF_NBS	41	53.0	6.7	57.1	30.0	57.1	
SF change*	41	5.6					0.003*

SF_NBS_BL: Social Functioning Norm-based Score Baseline; SF_NBS: Social Functioning Norm-based Score

Table: 18

Paired t-test: Change at Follow-up, Role Emotional

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
RE_NBS_BL	41	48.9	11.3	55.3	23.7	55.3	
RE_NBS	41	51.2	9.4	55.3	23.7	55.3	
RE change	41	2.3					0.298

RE_NBS_BL: Role Emotional Norm-based Score Baseline; RE_NBS: Role Emotional Norm-based Score

Table: 19

Paired t-test: Change at Follow-up, Mental Health

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
MH_NBS_BL	41	52.3	7.0	55.0	34.5	64.1	
MH_NBS	41	55.6	7.8	57.3	32.3	64.1	
MH change	41	3.3					0.008

MH_NBS_BL: Mental Health Norm-based Score Baseline; MH_NBS: Mental Health Norm-based Score

Table: 20

Paired t-test: Change at Follow-up, Physical Component

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
PCS_BL	41	47.7	10.1	51.0	21.8	63.1	
PCS	41	48.4	9.9	52.2	19.8	60.3	
PCS change	41	0.7					0.704

PCS_BL: Physical Component Score Baseline; PCS: Physical Component Score

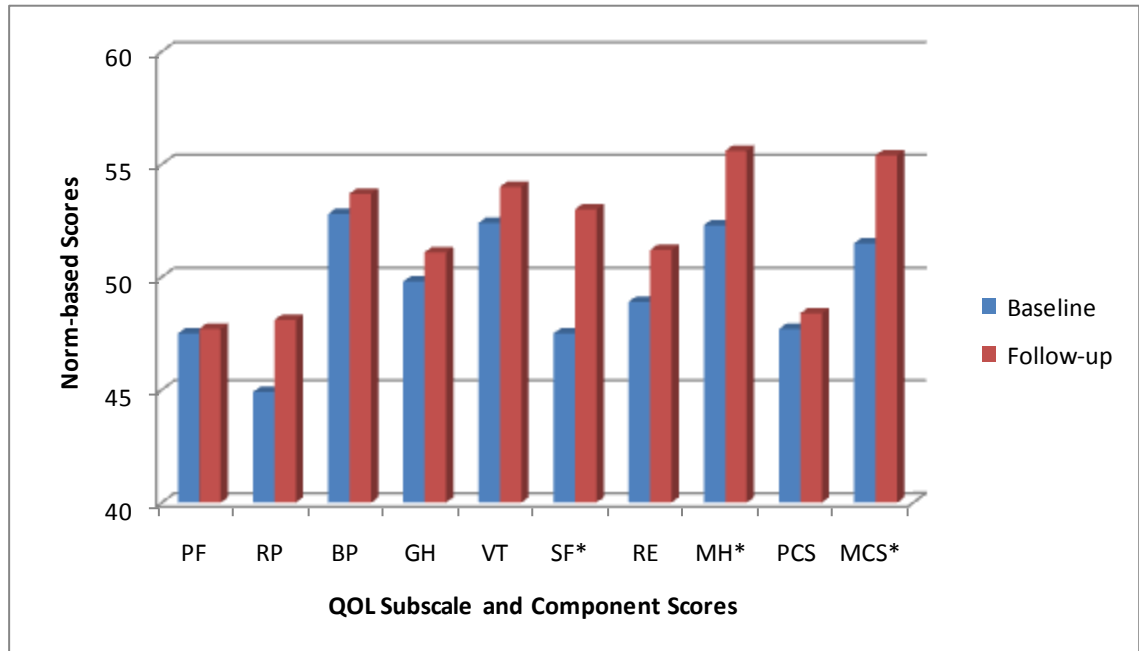
Table: 21

Paired t-test: Change at Follow-up, Mental Component

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	P-value
MCS_BL	41	51.5	8.2	53.1	35.7	67.0	
MCS	41	55.4	8.2	57.0	27.2	68.9	
MCS change	41	3.9					0.014

MCS_BL: Mental Component Score Baseline; MCS: Mental Component Score

Figure: 3
Changes in QOL Scores over Time



Note: PF = Physical Functioning; RP = Role Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role Emotional; MH = Mental Health; PCS = Physical Component Score; MCS = Mental Component Score

These paired t-tests were performed to assess change on all QOL subscales between time one (pre-procedure) and time two (follow-up). Exactly 50% of the participants ($n = 41$) had accessible baseline QOL pre-procedure data. Although the majority of the changes were not statistically significant, it is interesting to note that all change scores were positive (i.e., all baseline QOL mean scores were lower than 12+ month follow-up QOL scores). The magnitude of the changes was statistically significant for the SF ($p = 0.003$) scale, suggesting participants reported significantly improved social functioning as compared to pre-procedure. Although not significant at the conservative p -value established by the Bonferroni correction, the MH ($p = 0.008$) scale and the MCS ($p = 0.014$) differed significantly from baseline at the $p = 0.05$ level,

indicating improved mental health as compared to pre-procedure. Contrary to what was hypothesized, no significant changes were noted in the mean Physical Functioning, Role Physical, or Bodily Pain scores.

Research Question 3

Research question three was developed to examine the sleep quality of participants and the relativity of these sleep quality scores to the conservative cutoff score of eight suggested by Carpenter and Andrykowski (1998). In Tables 22-25, descriptive statistics, the lower and upper 95% confidence intervals for the percentage of participants at or above the clinical cutoff score of eight, and the results of a t-test comparing the PSQI mean with that of other populations originally used to determine the cutoff score of eight are outlined.

Table 22
Pittsburgh Sleep Quality Index Means

Variable	N	Mean	Std Dev	Minimum	Maximum
Sleep Quality	82	0.7	0.8	0.0	3.0
Sleep Latency	80	1.1	1.1	0.0	3.0
Sleep Duration	81	0.9	1.0	0.0	3.0
Habitual Sleep Efficiency	78	0.7	1.0	0.0	3.0
Sleep Disturbance	82	1.4	0.6	0.0	3.0
Use of Sleeping Medication	82	0.8	1.1	0.0	3.0
Daytime Dysfunction	82	0.7	0.7	0.0	2.0
Total PSQI	82	6.3	4.4	0.0	19.6

The mean PSQI score for participants was 6.3 ($sd = 4.4$), falling below the conservative cutoff score of eight. Global PSQI scores ranged from 0.0 to 19.6, however, suggesting variation in sleep quality within the sample.

Table 23
Pittsburgh Sleep Quality Index Frequencies

PSQI Total	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	1	1.22	1	1.22
1	6	7.32	7	8.54
2	9	10.98	16	19.51
2.3333	1	1.22	17	20.73
3	9	10.98	26	31.71
4	8	9.76	34	41.46
5	7	8.54	41	50.00
6	9	10.98	50	60.98
7	6	7.32	56	68.29
8	3	3.66	59	71.95
9	5	6.10	64	78.05
10	3	3.66	67	81.71
10.5	1	1.22	68	82.93
11	4	4.88	72	87.80
12	2	2.44	74	90.24
13	1	1.22	75	91.46
14	2	2.44	77	93.90
15	2	2.44	79	96.34
16	1	1.22	80	97.56
18.6667	1	1.22	81	98.78
19.6000	1	1.22	82	100.00

Within this sample, 31.70% of participants scored at or above the clinical cutoff of eight, indicating the presence of significant sleep disturbances within almost one third of the sample. The investigator hypothesized that the majority of the sample would have PSQI scores at or above the recommended clinical cutoff of eight. Prior to Carter and Andrykowski's (1998) work, a clinical cut score of five was used for the PSQI. It is interesting to note that this hypothesis would have been supported using this more liberal cutoff score. Contrary to what was hypothesized, however, using the more conservative

cutoff, only 31.70% of participants had scores of eight or higher. The majority of the participants, then, did not report significantly impaired sleep quality.

Table: 24

Pittsburgh Sleep Quality Index Cutoff Percentages and Confidence Intervals

Percentage at or Above Cutoff of 8	Lower 95% CI for Percentage at or Above 8 (alpha = 0.05)	Upper 95% CI for Percentage at or Above 8 (alpha = 0.05)
31.70%	21.6%	42.8%

A 95% confidence interval was established around the observed percentage of participants who scored at or above the recommended cutoff of eight. This 95% confidence interval ranged from 21.6% to 42.8%, suggesting that, if the study was conducted 100 times, the observed percentage of individuals scoring eight or higher would be expected to fall within this confidence interval at least 95 of those 100 times. This information also supports the rejection of the hypothesis that the majority of participants would have significantly impaired sleep functioning, using the clinical cut score of eight.

A t-test was completed in order to compare the mean PSQI scores of differing populations. The sample means and standard deviations were referenced in the Carpenter and Andrykowski (1998) article and subsequently utilized in these analyses. Carpenter and Andrykowski examined the psychometric characteristics of the PSQI with various populations and used the findings as the basis of their recommendation to move the clinical cut point of the PSQI to a more conservative level of eight, rather than five. Given that the mean scores in the Carpenter and Andrykowski (1998) samples were used

to establish this more conservative cutoff score, it seemed valuable to compare the current sample to those samples.

Table 25

T-test: Comparison of Pittsburgh Sleep Quality Index Mean Scores of Current Sample with Other Populations

Sample	N	Months post	Mean	Std Dev	p-value
CS+HIPEC	82	12+	6.3	4.4	-
Bone Marrow Transplant	155	60.0 post transplant	5.6	3.9	0.216
Renal Transplant	56	66.6 post transplant	7.6	4.4	0.090
Women w/ Breast Cancer	102	28.9 post Dx (at least 3 mo. Post Tx)	7.0	4.4	0.302
Women w/ Benign Breast Problems	159	-	6.4	4.2	0.905
Controls*		-	2.7	1.7	<0.001

Sample means and standard deviations published by Carpenter and Andrykowski (1998)

An examination of the *p*-values revealed that the sleep quality of CS+HIPEC survivors did not differ significantly from that of bone marrow transplant recipients, renal transplant recipients, women treated for breast cancer, or women with benign breast problems. The mean sleep quality was, however, significantly worse than that of healthy controls ($p = <0.001$).

Research Question 4

The purpose of research question four was to examine the relationships between global sleep quality scores, the QOL subscale and component scores, age at CS+HIPEC, and months since procedure (all continuous variables). The correlation matrix is presented in Table 26.

Table 26

Pearson Correlation Coefficients: Sleep Quality and Quality of Life

	HIPEC_age	time_since_surgery	PF_NBS	RP_NBS	BP_NBS	GH_NBS
HIPEC_age	1.000	-0.020	-0.270	-0.290	-0.098	-0.109
	0.859	0.859	0.015	0.009	0.387	0.335
	81	81	81	80	81	81
time_since_surgery	-0.020	1.000	-0.032	-0.058	-0.005	-0.017
	0.859	0.779	0.612	0.966	0.966	0.880
	81	81	81	80	81	81
PF_NBS	-0.270	-0.032	1.000	0.747	0.556	0.603
	0.015	0.779	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
RP_NBS	-0.290	-0.058	0.747	1.000	0.642	0.628
	0.009	0.612	<.001	<.001	<.001	<.001
	80	80	81	81	81	81
BP_NBS	-0.098	-0.005	0.556	0.642	1.000	0.564
	0.387	0.966	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
GH_NBS	-0.109	-0.017	0.603	0.628	0.564	1.000
	0.335	0.880	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
VT_NBS	-0.183	0.050	0.628	0.751	0.601	0.731
	0.102	0.657	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
SF_NBS	-0.174	-0.059	0.640	0.668	0.603	0.634
	0.121	0.600	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
RE_NBS	-0.153	-0.039	0.572	0.633	0.530	0.619
	0.173	0.731	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
MH_NBS	-0.101	-0.078	0.360	0.554	0.376	0.521
	0.369	0.490	0.009	<.001	0.001	<.001
	81	81	82	81	82	82
PCS	-0.248	-0.013	0.890	0.866	0.778	0.736
	0.026	0.907	<.001	<.001	<.001	<.001
	81	81	82	81	82	82
MCS	-0.090	-0.044	0.340	0.516	0.410	0.603
	0.422	0.698	0.002	<.0001	0.000	<.001
	81	81	82	81	82	82
psqi_tot	0.133	-0.052	-0.417	-0.485	-0.453	-0.340
Total PSQI	0.238	0.648	<.001	<.001	<.001	0.000
	81	81	82	81	82	82

	VT_NBS	SF_NBS	RE_NBS	MH_NBS	PCS	MCS	psqi_tot
HIPEC_age	-0.183	-0.174	-0.153	-0.101	-0.248	-0.090	0.133
HIPEC_age	0.102	0.121	0.173	0.369	0.026	0.422	0.238
	81	81	81	81	81	81	81
time_since_surgery	0.050	-0.059	-0.039	-0.078	-0.013	-0.044	-0.052
	0.657	0.600	0.731	0.490	0.907	0.698	0.648
	81	81	81	81	81	81	81
PF_NBS	0.628	0.640	0.572	0.360	0.890	0.340	-0.417
	<.001	<.001	<.001	0.001	<.001	0.002	<.001
	82	82	82	82	82	82	82
RP_NBS	0.751	0.668	0.633	0.554	0.866	0.516	-0.485
	<.001	<.001	<.001	<.001	<.001	<.001	<.001
	81	81	81	81	81	81	81
BP_NBS	0.601	0.603	0.530	0.376	0.778	0.410	-0.453
	<.001	<.001	<.001	0.001	<.001	0.000	<.001
	82	82	82	82	82	82	82
GH_NBS	0.731	0.634	0.619	0.521	0.736	0.603	-0.400
	<.001	<.001	<.001	<.001	<.001	<.001	0.000
	82	82	82	82	82	82	82
VT_NBS	1.000	0.709	0.598	0.592	0.739	0.700	-0.521
		<.001	<.001	<.001	<.001	<.001	<.001
	82	82	82	82	82	82	82
SF_NBS	0.709	1.000	0.662	0.434	0.688	0.675	-0.270
	<.001		<.001	<.001	<.001	<.001	0.014
	82	82	82	82	82	82	82
RE_NBS	0.598	0.662	1.000	0.597	0.536	0.832	-0.425
	<.001	<.001		<.001	<.001	<.001	<.001
	82	82	82	82	82	82	82
MH_NBS	0.592	0.434	0.597	1.000	0.338	0.843	-0.456
	<.001	<.001	<.001		0.002	<.001	<.001
	82	82	82	82	82	82	82
PCS	0.739	0.688	0.536	0.338	1.000	0.341	-0.452
	<.001	<.001	<.001	0.002		0.002	<.001
	82	82	82	82	82	82	82
MCS	0.700	0.675	0.832	0.843	0.341	1.000	-0.410
	<.001	<.001	<.001	<.001	0.002		0.000
	82	82	82	82	82	82	82
psqi_tot	-0.521	-0.270	-0.425	-0.456	-0.452	-0.410	1.000
Total PSQI	<.001	0.014	<.001	<.001	<.001	0.000	
	82	82	82	82	82	82	82

Abbreviations: PF_NBS = Physical Functioning Norm-based Score; RP_NBS = Role Physical Norm-based Score; BP_NBS = Bodily Pain Norm-based Score; GH_NBS = General Health Norm-based Score; VT_NBS = Vitality Norm-based Score; SF_NBS = Social Functioning Norm-based Score; RE_NBS = Role Emotional Norm-based Score; MH_NBS = Mental Health Norm-based Score; PCS = Physical Component Score; MCS = Mental Component Score

In Table 26, the Pearson Correlation Coefficients between the global sleep quality scores, QOL subscale and component scores, CS+HIPEC age, and months since procedure for the entire sample are presented. Given that a higher score on the PSQI indicates the presence of more sleep quality problems (not desirable), while a higher QOL score indicates better QOL (desirable), a negative correlation in this analysis actually signified the expected relationship between the variables. As hypothesized, all of the QOL subscales were related significantly to PSQI scores. Among these correlations, the strongest relationship existed between sleep quality and the Vitality subscale ($r = -0.52, p < .001$). This relationship of moderate strength indicated that as sleep quality improved, vitality also improved (i.e. energy levels increased and signs of fatigue diminished). In conclusion, hypothesis four was accepted.

Also of note in these interrelationships were the significant negative relationships between age at CS+HIPEC and the Physical Functioning ($r = -0.27, p = 0.02$), Role Physical ($r = -0.29, p = 0.01$), and Physical Component ($r = -0.25, p = 0.03$) scores. These findings suggest that as age increased, physical functioning decreased. Similar findings would be anticipated in the general population. The number of months since surgery was not related significantly to the QOL scores.

Research Question 5

Hypothesis one.

In research question five, the investigator examined the respective contributions of resection status and primary tumor site to the overall Mental and Physical Component scores. Two separate two-way ANOVAs were run in order to examine the effects of these categorical variables on the component quality of life scores. Based on the demographics of the sample, some adjustments were made for the intended analyses. Specifically, R0 and R1 resection statuses were combined on account of inconsistent ratings and recordings by various surgeons within the database. Additionally, no individuals with R2c were represented within the sample. This was not surprising given that all participants had to be at least 12 months post-procedure, and R2c is the worst resection status ranking. Resection status categories, then, were R0/R1, R2a, and R2b. Additionally, individuals with an R2b resection status were present only in those with a primary diagnosis of appendiceal cancer. Finally, over sixty percent of the sample was composed of individuals with a primary diagnosis of appendiceal cancer, while the remainder of the primary diagnostic categories were much smaller. Therefore, participants who did not have a primary diagnosis of appendix cancer were grouped collectively as “other”.

Ultimately, two separate two-way ANOVAs were run in order to examine the contributions of the two independent, categorical variables (i.e. resection status and primary tumor site) to the respective QOL Physical and Mental Component scores. Specifically, the full models (with the main effects and interaction) were run first.

Results for both were not significant, so the models were rerun without the interactions. The results of the analyses for research question five are presented in Tables 27-28. Specifically, the models without interactions are presented. Parameters for these models without interactions are in Appendix D (Tables M-N).

The first hypothesis for research question five was that patients who achieved a better resection status would have higher QOL scores at 12 or more months. There was no significant main effect of resection status on the Physical Component $F(2, 76) = 0.48$, $p = 0.619$ (Table 27) or Mental $F(2, 76) = 0.41$, $p = 0.667$ (Table 28) scores. This hypothesis, therefore, was not accepted.

Although resection status did not produce significant main effects in this model, primary tumor site produced a significant main effect on the Physical Component Scores of the participants $F(1, 76) = 4.00$, $p = 0.049$.

Table 27
Analysis of Variance: Physical Component Scores, No Interaction

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	468.018	156.006	1.41	0.245
Error	76	8382.521	110.296		
Corrected Total	79	8850.539			

R-Square	Coeff Var	Root MSE	PCS Mean
0.053	22.292	10.502	47.111

Source	DF	Type III SS	Mean Square	F Value	Pr > F
site	1	441.329	441.329	4.00	0.049
resect	2	106.356	53.178	0.48	0.619

Table 28
Analysis of Variance: Mental Component Scores, No Interaction

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	61.549	20.516	0.28	0.837
Error	76	5490.672	72.246		
Corrected Total	79	5552.221			

R-Square	Coeff Var	Root MSE	MCS Mean
0.011	15.810	8.500	53.763

Source	DF	Type III SS	Mean Square	F Value	Pr > F
site	1	0.034	0.034	0.00	0.983
resect	2	58.895	29.448	0.41	0.667

Hypothesis two.

The second hypothesis for research question five was that patients with a primary diagnosis of cancer of the appendix or pseudomyxoma peritonei (PMP) would demonstrate higher QOL component scores at 12 or more months than their counterparts. First of all, only one individual with a primary diagnosis of PMP was represented in the sample, making it impossible to perform any analyses or extrapolate conclusions based on this primary diagnostic group. The one individual with a diagnosis of PMP was

included in the “other” group. The large number of individuals with a primary diagnosis of appendix cancer, however, permitted analyses and comparisons with this “other” group.

A t-test was used to compare the group means of the appendiceal and “other” group. Upon comparison of the QOL PCS and MCS of members of the appendiceal and “other” group, it was not possible to accept this second hypothesis for research question five. The global QOL scores of the members of the appendiceal group did not differ significantly from those of the “other” group (PCS, $p = 0.0993$; MCS, $p = 0.8776$), possibly due, at least in part, by the necessary collapsing of non-appendiceal groups into an “other” category. Please refer to Tables 29-30 for these analyses. Similarly, no significant differences ($p = 0.099$) existed between the QOL PCS of those in the appendiceal group ($m = 48.671$) and those in the “other” group ($m = 44.630$), nor between the QOL MCS of those in the appendiceal group ($m = 53.897$) and those in the “other” group ($m = 53.596$) ($p = 0.878$). In conclusion, neither hypothesis for research question five was supported.

Table: 29
Physical Component Scores for Appendiceal and “Other” Groups

site	N	Mean	Std Dev	Std Err	Minimum	Maximum
appendiceal	52	48.671	9.632	1.336	22.880	60.100
other	29	44.630	11.780	2.191	19.770	60.310
Diff (1-2)		4.041	10.452	2.422		

Method	Variances	DF	t Value	Pr > t
Pooled	Equal	79	1.67	0.099
Satterthwaite	Unequal	48.965	1.57	0.122

Equality of Variances				
Method	Num DF	Den DF	F Value	Pr > F
Folded F	28	51	1.50	0.206

Table: 30
Mental Component Scores for Appendiceal and “Other” Groups

Site	N	Mean	Std Dev	Std Err	Minimum	Maximum
appendiceal	52	53.897	7.851	1.089	27.240	66.060
other	29	53.596	9.280	1.723	25.910	68.910
Diff (1-2)		0.300	8.386	1.943		

Method	Variances	DF	t Value	Pr > t
Pooled	Equal	79	0.15	0.878
Satterthwaite	Unequal	50.403	0.15	0.886

Equality of Variances				
Method	Num DF	Den DF	F Value	Pr > F
Folded F	28	51	1.40	0.296

CHAPTER V

CONCLUSIONS

Overview

In this chapter, implications of the findings are described. Limitations of this study, implications for the counseling profession, and suggestions for future research also are offered.

Discussion

This study represents an important contribution to the literature base concerning survivors of CS+HIPEC. Given the paucity of adequately sized behavioral health investigations of members of this population, the addition of this study with its satisfactorily large number of participants permits the researcher to analyze data collected from survivors who had an array of disease and treatment experiences and allows readers to make generalizations from the findings with more confidence.

First of all, an examination of the descriptive statistics permits useful generalizations about the population. Aside from the lack of heterogeneity relative to race and ethnicity, two key features of the descriptive statistics are noteworthy: the number of long-term survivors with each of the respective primary diagnoses as well as the number of individuals with each resection status. Over sixty percent of the sample consisted of individuals with a primary diagnosis of cancer of the appendix, suggesting

that individuals with a primary diagnosis of cancer of the appendix had the strongest representation among long-term CS+HIPEC survivors. Similar findings related to the overrepresentation among long-term survivors of individuals with a primary diagnosis of cancer of the appendix are supported in the literature. Levine et al. (2007) noted the differential clinical outcomes experienced by patients based on the pathological characteristics of their primary diagnosis and concluded that primary tumor site is correlated with improved survival. Specifically, these researchers noted the tendency for patients with low grade peritoneal surface disease, including appendiceal cancer, to experience more desirable (i.e. longer) clinical outcomes than those with higher grade disease. It is not surprising, then, to find that 60% of the current sample of long-term survivors had a primary tumor site of appendix.

Also noteworthy in the descriptive statistics was the percentage of participants with each designated resection status. Again, 60% of the sample had an R0/R1 resection status, 30% had an R2a resection status, and 10% had an R2b resection status. None of the long term survivors had an R2c resection status, and R2b statuses were represented strictly within the appendiceal group, not in the “other” group. This finding is similar to that of Levine et al. (2007) who reported that resection status was correlated significantly with improved survival status and that patients who experienced a complete resection (i.e. R0/R1) had better outcomes than their counterparts who had incomplete resections, regardless of primary diagnosis. In fact, Levine et al. (2007) recommended that those patients whose surgeons do not believe that an R2a resection status (or better) is feasible should consider foregoing this major procedure and all of its potential complications. In

their review of procedures, three year survival rates for those with an R2c resection status was 14.0% (+/- 4.2), 15% (+/- 5.3%) for those with an R2b status, 38.7% (+/- 5.3%) for those with an R2a status, and 59.9% (+/- 3.9%) for those with an R0/R1 resection status. It is not surprising, then, to find this 60%, 30%, and 10% breakdown of R0/R1, R2a, and R2b resection statuses within the current sample, the dearth of R2c statuses, and the presence of individuals with an R2b status strictly within the group with the best prognosis (i.e. the low grade appendiceal group).

Although potentially associated with improved survival estimates, resection status did not have a significant main effect on overall physical and mental component scores within this sample. Tuttle et al. (2006) reported similarly that resection status was not a significant contributor to QOL scores within their cohort of patients at the University of Minnesota Cancer Center. From these findings, one can conclude that while resection status may be associated with extended survival, it is not associated necessarily with QOL ratings among those who do survive for extended periods of time.

Many additional noteworthy findings related to the quality of life and sleep quality of survivors of CS+HIPEC can be gleaned from this study as well. First, the QOL subscale scores of participants revealed how they were functioning in a variety of domains as well as how they were functioning in comparison to the general population norms. The Physical Functioning subscale scores fell significantly below the general population norms, while the Mental Health and Mental Component scores were significantly higher than general population norms. Other scale scores were significantly different from the population norms at an alpha level of $p = 0.05$ yet did not differ at the

more conservative cut-off of $p = 0.005$ following the Bonferroni correction. For example, the Role Physical and Physical Component scores were significantly lower than population norms at the more liberal $p = 0.05$ level, while Vitality and Bodily Pain scores were significantly higher than population norms when utilizing this alpha level. Although these results were not considered significant for the purposes of this dissertation, it is important to underscore that differences may exist between the scores of CS+HIPEC survivors and those of the general population within these respective subscales. The remainder of the subscale scores (general health, role emotional, and social functioning) did not differ significantly from those of the general population.

In a previous study, McQuellon et al. (2007) reported that all (minus the Vitality) subscale scores in their sample, despite significant improvement between baseline to 12 months, remained significantly lower than the population norms. Within the current sample, however, solely the Physical Functioning scores were significantly lower than the population norms, while the remainder of the scores did not differ significantly or were comparatively higher. The substantial differences in months since procedure (i.e. 12 months in the McQuellon et al. (2007) participants versus a range of 13-180.2 months in the current study) may contribute to these discrepancies. The findings from this sample are in closer alignment to those of Schmidt et al. (2005), who found that in their sample of long-term survivors (mean years since treatment = 4, range = 1-8), the Physical ($p = 0.04$), Role ($p = 0.002$), and Social Functioning ($p = 0.001$) scores were significantly impaired relative to those of the general Norwegian population, while the Emotional and Cognitive Functioning scores did not differ significantly. Given the small sample size (N

= 20) of Schmidt et al. (2005), interpretations should be made with caution, yet the physical impairments and *lack* of emotional impairments were similar to the findings in the current study. Unlike the Schmidt et al. (2005) group, however, the current sample did not describe significantly impaired Social Functioning, and the Mental Health scores of the participants were not merely in line with the population norms; they were, in fact, significantly higher. In conclusion, unlike the findings in some previous studies, the current group was not functioning lower than their general population counterparts in *every* QOL domain. Rather, strictly their physical functioning was significantly lower. Their reported mental health was actually significantly better.

Although it is impossible to draw explanatory conclusions from these data, it is possible to speculate cautiously as to why this sample differed from others described in the literature relative to their high Mental Health scores. First of all, it is important to remain mindful of who composed the sample and why other prospective participants were not represented. McQuellon et al. (2007) noted that those who are not represented in these post-procedure psychosocial studies are not missing at random. It is likely that those who do not participate are dead or experiencing significant physical and/or psychological difficulties, ultimately leaving the healthiest individuals who experienced optimal outcomes to participate. The more complicated and lachrymose trajectories, then, are likely not included in these datasets, and the data may be colored with a rosier disposition.

In addition to being the best-case scenarios within their cohort, all of these participants shared at least a semblance of the same experience in that they traversed

through a mortal time zone (McQuellon & Cowan, 2007). Although most humans recognize that death is a constant, inescapable companion throughout life, these survivors, upon receiving notification of their aggressive diagnoses, were forced to figuratively waltz with death (Pinkola Estes, 1990) within this mortal time zone. That is, they were presented with the stark possibility of fast approaching death. Arguably, reception of such an aggressive diagnosis brought to them awareness of core existential issues, including finitude of mortality and solitude. Additionally, such a quickening of the dance pace may have brought about an acute awareness and new perspective of life. These survivors, whose dance pace has receded once more, may carry with them a keen awareness of the inevitability of death and its ability to lead. A renewed appreciation for extended life and health may be a by-product of this rendezvous.

Along these same lines, numerous researchers have investigated concepts dealing with positive internal changes that result within humans following trauma and adversity. Referred to as post-traumatic growth, Calhoun and Tedeschi (1998), for example, described the gradual internal paradigm shifts that may occur following internal disruption spurred by trauma. Enhancement of self regard, life appreciation, life philosophy, and personal relationships are only a few of these areas that may be susceptible to gradual growth post-trauma.

Similarly, other investigators (e.g. Sprangers and Schwartz, 1999) have examined a concept referred to as response shift. The idea behind response shift is that humans are adept at accommodating to their new norms. New experiences bring about shifts in internal standards and conceptualizations. Within this population, the months

immediately post-procedure might have brought about significant suffering and life quality reductions, prompting a response shift. As healing began to occur, however, life norms and expectations might have increased as well, producing an additional response shift. Compared to their immediate post-treatment quality of life, these survivors may perceive their current quality of life, including mental health, as relatively high. Their perception of and appreciation for life may have changed.

In conclusion, numerous factors may have contributed to the observed Mental Health scores that were significantly higher than the population norms. The participants of this study were, by nature, the best case scenarios of the group. Their intimate confrontations with mortal time, post-traumatic growth, and response shift may be additional contributing factors. It is important to remember that these suggestions, however, are merely speculations, and that more research is needed to assess the veracity of these speculations.

The contributing roles of surgical and physiological variables to long-term QOL scores also were examined. As mentioned previously, resection status did not produce significant effects on Physical and Mental Component scores, contrary to what was hypothesized. Primary tumor site, however, did demonstrate a significant main effect on the Physical Component scores of survivors. Specifically, a primary diagnosis of cancer of the appendix yielded a significant positive effect on the long-term Physical Component scores of survivors. An examination of the score parameters helps to clarify this effect. Holding all other variables constant, individuals with a primary diagnosis of cancer of the appendix can anticipate a long-term physical quality of life score this is, in general, 5.095

units higher ($p = 0.049$). From these findings, it is possible to conclude that CS+HIPEC candidates who have a primary diagnosis of cancer of the appendix may experience benefits in their long-term physical quality of life on account of having this, rather than alternate, primary diagnosis.

In addition to site and resection status, physical quality of life scores were examined in relation to certain demographic variables, including age at the time of procedure. Pearson correlations revealed significant, albeit weak, negative relationships between CS+HIPEC age and Physical Functioning, Role Physical, and Physical Component scores. As age at time of procedure increased, physical functioning and quality of life tended to decrease in survivors. Similar relationships between age and these physical variables could be expected within members of the general population as well, however. Interestingly, months since surgery was not associated significantly with QOL scores.

Changes between baseline and long-term follow-up scores were examined as well in order to gain insight into movement within QOL functioning domains over time. All change trends were positive, yet only Social Functioning scores demonstrated significant change over time. Although not significant at the $p = 0.005$ level, the Mental Health subscale and Mental Component scores differed from baseline at a less conservative p -value (i.e. $p = 0.05$). Other researchers also have examined movement over time within subscale scores, with this movement highlighted best within longitudinal studies. Similar to the findings in the current study, McQuellon et al. (2001) reported a significant overall effect on emotional ($p < 0.001$), physical ($p = 0.003$), and functional ($p = 0.004$) well

being, with scores decreasing immediately post-procedure and then increasing, relative to baseline, at three, six, and twelve months. In a later study, McQuellon et al. (2007) reported a significant overall effect from baseline to the 12 month time point, with physical functioning ($p = 0.001$), role physical ($p = 0.016$), and bodily pain ($p = 0.001$) scores improving significantly. Within their group, social functioning consistently remained high and did not fluctuate significantly. Additionally, they noted that 24% of the sample endorsed significant depressive symptoms at 12 months post-procedure. Similarly, Tuttle et al. (2006) reported significant improvement between baseline and 12-month emotional well being ($p = 0.003$) and functional well-being ($p = 0.003$), yet no significant improvement in social functioning from baseline to 12-month follow-up. Finally, McQuellon et al. (2003) reported significant improvement between baseline and long-term follow-up in the functional ($p = 0.01$) and physical ($p = 0.05$) well being scores, yet not in emotional or social well being scores.

A review of these study findings highlights the typical QOL score trends for members of this population. Many researchers have noted that scores tend to drop immediately post-procedure and then improve over time, relative to baseline levels. Scores typically remain, however, below those of the population norms. Researchers have reported different findings relative to what subscale scores change over time, yet most found significant change in the physical and functional subscale scores and no significant change in social functioning. Findings around emotional well being scores have been mixed. Within the current study, and unlike previous findings, the Physical Functioning scores did not change significantly between baseline and long-term follow-

up measures. These scores did, however, remain below the population norms. Also dissimilar to previous findings (e.g. McQuellon et al., 2007; Tuttle et al., 2006), the Social Functioning scores demonstrated significant improvement over time. The Mental Health scores also improved over time, ultimately exceeding the population norms.

Again, explanations regarding these trends should be offered and interpreted as speculation, yet it is possible to offer some hypotheses regarding these trends. Regarding the lack of significant movement with the physical subscale scores, it is possible that these survivors have endured many lasting physical complications and functional detriments, hindering significant improvement from baseline levels. Also, it is possible that these scores did, in fact, improve significantly for a window of time but have gradually or suddenly declined with the development of new complications or advancing age. In this regard, it bears repeating that survivors were surveyed at an array of times throughout their recovery trajectories.

Regarding the significant improvements in Mental Health and Social Functioning over time, it is possible that any of the aforementioned constructs, including post-traumatic growth and response shift, were at work. Additionally, it is also possible that, in the time frame prior to the extensive procedure, participants reported significant distress and social withdrawal, thereby lowering these scores. After progressing successfully through the hospitalization and recuperation time frames, it is possible that Mental Health and Social Functioning rose in tandem. From cross-sectional data, however, it is impossible to discern the reasoning behind these trends.

Additional contributions to the literature base provided by this study include the findings related to sleep quality. To the investigator's knowledge, no comprehensive sleep quality studies have been performed with members of this population, yet some previous investigators have noted the existence of symptoms related to sleep quality. For example, Schmidt et al. (2005) reported that fatigue and insomnia were among the top three symptoms reported by survivors. Findings from the current study represent a more comprehensive examination of such symptoms and provide a foundation on which to build future investigations.

Contrary to what was hypothesized, the mean sleep quality score in this study ($m = 6.3$) was below the conservative clinical cut-off of eight that marks the presence of significant sleep quality impairments. A t-test to compare this sample mean with that of other populations (i.e. bone marrow transplant, women treated for breast cancer, renal transplant patients, and women with benign breast problems) did not reveal any significant differences, while differences did exist between the mean score for this group and that of a group of healthy controls ($p < 0.001$) (Carpenter & Andrykowski, 1998). These findings suggest that CS+HIPEC survivors experience sleep quality similar to that of other cancer and treatment populations but worse than that of controls. Despite this mean score below the clinical cutoff, however, almost one third of the sample (31.70%) endorsed clinically significant levels of sleep quality impairments. With approximately one third of individuals reporting clinically significant sleeping problems, even using a conservative clinical cutoff score, ongoing assessment of sleep quality with patients and further research on sleep-related issues among this population is warranted.

Providing additional support for future sleep quality studies and interventions are the significant positive relationships found between global sleep quality and various QOL scores. The strongest relationship, a correlation of moderate-strength ($r = 0.521, p < 0.001$), was found between global sleep quality and Vitality. These findings are not surprising, given that the vitality QOL subscale assesses levels of energy and fatigue. The comparatively weakest relationship, albeit statistically significant, existed between global sleep quality and social functioning ($r = 0.270, p = 0.01$). In addition to revealing the magnitude of the relationships between these constructs, these findings also underscore the importance of adopting a biopsychosocial model of care with patients. These correlations suggest the presence of significant interrelations among the various domains of health, including physical, mental, and social health. From this investigation, it is evident that sleep quality is related to all of the aforementioned domains. The adoption of an integrative model and approach to care encourages any practitioner to consider the functioning of all domains of health.

Overall, results from this investigation demonstrate that long-term survivors can achieve desirable quality of life. Physical Functioning remained below what is normal for the general population, yet other QOL domains were no different, or even better, than the general population levels. Mental Health scores were higher than those expected within the general population. Additionally, the long-term survivors in this investigation reported significant improvement in Social Functioning and Mental Health as compared to baseline. Approximately one third of participants reported impaired sleep quality. The descriptive statistics revealed the overrepresentation of individuals with a primary

diagnosis of appendiceal cancer, suggesting the more favorable pathological characteristics of this primary diagnosis within the group. Similarly, site of primary tumor origination had a significant main effect on long-term Physical Component scores. Likewise, the paucity of long term survivors with an R2c resection status designation suggests its comparatively poor survival prognosis. Individuals with R2b status were found only within the appendiceal group.

Although these findings and associated generalizations are of great use, a point highlighted by McQuellon et al. (2007) bears significant weight here as well. McQuellon et al. (2007) noted that “mean scores can mask considerable individual variability” (p. 1112), suggesting that although these statistics yield averages relative to how the group is functioning collectively, much individual variation exists. Every survivorship journey is unique, and those functioning on considerably lower levels must not be forgotten or masked by means. In other words, statistical significance must not overshadow clinical significance. Group analyses may not reveal findings of statistical significance, yet the human suffering of one patient carries great clinical significance that must not be overlooked.

Limitations of the Study

Although results of this study represent an important contribution to the literature concerning survivorship post-CS+HIPEC, some limitations of the study should be noted. First, participants of this study represented a convenience sample of individuals from not only a solitary medical institution but also patients of a small number of surgeons, thereby limiting generalizability. Similarly, in spite of the investigator’s attempt to limit

exclusion criteria in order to capture the stories of as many survivors as possible, those who participated were those who had up-to-date contact information through the hospital, were in adequate health to complete the survey in a timely fashion, and, of course, were still living. Information from those who did not live at least 12 months after the surgery, were lost to follow-up, or who were too ill to complete the instruments, therefore, was not represented, suggesting that participants in this study represented those with optimal outcomes.

Similarly, despite attempts to obtain a heterogeneous and inclusive sample, the sample was rather homogenous, as evidenced by the ethnic, racial, primary diagnosis, and resection status statistics. The sample, for example, largely consisted of white, non-Hispanic individuals, all but one with insurance. This lack of heterogeneity reduces the generalizability of the study, and analyses in the current study had to be adjusted accordingly (e.g. due to insufficient numbers of individuals with a variety of primary diagnoses, the participants were classified into the primary diagnosis categories of “appendix” or “other” for the purposes of the analysis). Also of note was the fact that a number of individuals (approximately eight) did not complete and return the consent forms with their packets. All of these data were lost, and the possibility that these individuals differed in some way from the remaining participants who did return consent forms could not be ruled out.

An additional sampling limitation was related to the fact that baseline (i.e., pre-procedure) data was not available for all participants. Rather, baseline QOL data was available for only a subset of participants ($n = 41$). Given that these pre-CS+HIPEC

QOL data were acquired in a previous research investigation in which only a percentage of the current participants took part, changes in QOL scores over time could be assessed only in a portion of the participants. It is unknown to what extent this would generalize to all participants in the study.

Further, it is important to remain mindful of the limitations of any cross-sectional research when reviewing the results of this study. Data was collected at one time point along the recovery trajectory for these individuals. Previous research studies with these survivors demonstrated significant changes in QOL scores across the recovery trajectory, with lowest scores reported during those months immediately post-procedure (e.g. McQuellon et al., 2001). Changes across the recovery trajectory cannot be ascertained from this dataset, meaning significant decreases or increases in QOL or sleep quality during alternate timeframes may not be captured. Rather, a single snapshot of how these individuals are faring was obtained.

Finally, “noise”, in the form of uncontrolled variables, existed within this dataset. To clarify, participants in the full study ranged from 13 to 180.2 months post-CS+HIPEC. Although the number of months post-procedure was one variable considered in the analyses, it is possible that ancillary factors, unrelated to the CS+HIPEC procedure, may have impacted the QOL scores. Measures could not be taken to control for each of these potential contributing factors, and no control group was available for comparison purposes. McQuellon et al. (2003) highlighted this limitation as well, stating, “One vexing problem facing QOL researchers conducting long-term follow-up studies is to what extent a disease process and subsequent treatment have affected the

patient's overall well-being compared with what changes in QOL would have occurred during the normal process of aging" (p. 161). In order to clarify the role of the disease and treatment, score comparisons were made to available population norms and to baseline data for those participants (50% of total sample) on whom it was available. It remains important however, when interpreting the results, to acknowledge the contributions of an array of other variables potentially impacting the reported QOL scores.

Implications for Counseling

This study represents an important addition to the body of literature concerning CS+HIPEC recipients. Few studies with sufficiently large sample sizes have been conducted with long-term survivors of CS+HIPEC. By acquiring data from a larger number of survivors, readers, including counselors who work with members of this population, become able to make generalizations from the results more confidently. Findings from this research investigation therefore have numerous implications for counselors working with patients and survivors of CS+HIPEC.

First of all, results from the QOL assessments revealed how the QOL scores of survivors compared to those of the general population. This multidimensional QOL data informs those who work with these survivors of how these individuals may be functioning in an array of domains, thereby enhancing practitioners' conceptualization and treatment plans. From this dataset, one can note that survivors' physical functioning was significantly worse in comparison to that of the general population, while their mental health was, as a group, significantly better. As a counselor focusing on the mental

health of patients and survivors, these findings are heartening; yet it is important to take note of the variation within the scores. Upon examination of the range in the Mental Health subscale scores (e.g. 32.3 - 64.1) and Mental Component scores (e.g. 25.9 - 68.9), it is evident that some survivors reported Mental Health that was significantly impaired, with scores more than two standard deviations below the mean. This variation and range of scores held true for all QOL domains, including Social Functioning and Vitality. These ranges should remind practitioners of the need to be mindful of the *clinical* significance of findings and the importance of individual assessment.

Within their cancer journeys, it is possible that patients will experience both distress and growth of varying sorts. For example, it is possible that positive, strength-based aspects of life after trauma may be evident among members of this population (as evidenced by their Mental Health scores that were significantly higher than general population norms). Counselors who, by training, also have a strength and wellness-based focus, may take particular interest in investigations of and clinical work with positive growth after adverse experiences. These relatively high Mental Health scores serve as reminders to assess and clinically tend to both negative and positive experiences within members of this population.

Additionally, the analysis examining the significance of change between baseline and follow-up scores revealed that Mental Health and Social Functioning QOL scores improved significantly as compared to baseline levels. These findings suggest that, as a group, CS+HIPEC patients may experience more distress around the time of surgery than one or more years post-surgery. Based on these findings, the considerations for

counselors, then, include how to screen patients and survivors so that those in need of counseling and QOL assistance (e.g. those whose scores fall one standard deviation below the population mean) become evident and when, throughout this survivorship trajectory (e.g. immediately pre- and post-procedure), are counseling services in highest demand. Screening thresholds and survivorship plans, including mental health counseling, could be developed for survivors in need, with this data serving as a first step towards those efforts.

Additionally, prior to this study, the principal investigator was unable to locate any comprehensive assessments of the sleep quality of CS+HIPEC patients or survivors. Results of this study provide some preliminary evidence that a significant percentage of CS+HIPEC survivors (i.e. 31.70%) reported significant sleep quality impairments. Such findings suggest the potential utility of sleep quality assessments and interventions within this population. The significant relationships found between sleep quality and both Mental Health and Role Emotional QOL in survivors also bolsters the importance of assessing and tending to both sleep quality and emotionality.

The specific findings obtained from this study, such as those mentioned above, undeniably are important. Yet McQuellon et al. (2007) made a vital point relative to making generalizations from a quantitative study performed with members of this population. While extrapolations based on large amounts of aggregated data undoubtedly have their importance, human exceptions to these trends that are based on results from such analyses inevitably exist as well. While some patients may recover more quickly and demonstrate higher QOL scores than the means presented in this, or other, studies,

others will take much longer, if ever, to reclaim a life of acceptable quality (McQuellon et al., 2007). This reminder is essential, especially for those seeking to underscore the implications for counseling from this study. Individuals who undergo this procedure have unique experiences that include varying balances of physical and mental challenges and growth. Possibly more so than others, counselors are cognizant of this individuality and uniqueness in a person's experience and such uniqueness remains in existence in these experiences in mortal time. So, while this data may serve to help establish generalizations and time points when members may be most in need of therapeutic services, the unique needs and experiences of each person must not be overlooked.

Finally, from a broader vantage point, this research investigation highlights the important roles and niches that mental health counselors are able to fill within a medical setting. In addition to the specific research findings, the dissertation itself serves as an example of the importance of conducting social science research within medical settings and the need for availability of counseling services for these patients. Many patients navigating this setting are in need of attention to mental health and quality of life, two major foci of counselors.

Suggestions for Future Research

Suggestions for future research may be gleaned from the findings of this study. Long-term survivors of CS+HIPEC communicated QOL deficits related to physical functioning, and a significant percentage of these survivors reported poor sleep quality. Future researchers are encouraged to examine the factors that contribute to and maintain these impairments. Qualitative and mixed-methods studies may, in particular, help us

understand more fully the diversity of experiences. Additionally, despite their diagnoses and intensive procedures, this group of long-term survivors reported significantly higher Mental Health and Vitality QOL scores than their general population counterparts. These findings may underscore the existence or role of response shift (e.g. Sprangers & Schwartz, 1999), post-traumatic growth (e.g. Calhoun & Tedeschi, 1998), resilience, or a number of alternate strength-based factors that warrant future research.

Next, the quantitative data obtained in this, and previous studies, can serve as the groundwork on which to build future interventions with these patients. Specifically, this quantitative data informs researchers' and clinicians' understanding of issues of salience (e.g. sleep quality), the percentage of patients who experience said issues, and how the percentage of patients who struggle with these respective issues varies over time. In future studies, researchers should continue to collect longitudinal data, assessing how patients with differing primary diagnoses fare over time. Such data, in addition to serving as a reference for future candidates for the procedure and those working with this population, should ultimately inform intervention studies. The investigator was unable to locate any research detailing intervention studies with this population. Future interventions could take the form of pre-operative consultations, in-hospital interventions, or post-operative interventions and could be comprehensive (e.g. attention to mental health, pain management, nutrition, and spirituality, among others) or focused symptom management interventions. For instance, results from this quantitative study demonstrated that a significant percentage of long-term survivors may benefit from interventions designed to enhance sleep quality. Such intervention studies are a logical

next step within this research base, and quantitative data collected from members of this population can serve as support for their need and potential utility.

Finally, despite attempts to limit the number of exclusion criteria to the study, these participants still represented the best case scenarios- those individuals who lived at least 12 months post-procedure and were sufficiently healthy to complete the questionnaires. Similar to previous research investigations, the stories of those who did not fare as well remained excluded. Likewise, the uniqueness inherent in these hospitalizations, recovery trajectories, and overall experiences may not be uncovered sufficiently when data are aggregated in quantitative studies. A qualitative methodology, in which in-depth interviews with a smaller number of patients both during and post-hospitalization, may permit the researcher to capture the stories and attributed meaning of a wider spectrum of patients (i.e. those patients who experience ideal and poor outcomes as well as everything in between). Such a methodology would permit these patients to discuss in more detail personal issues of salience, thereby enriching this research body in a manner that may be especially useful for individuals considering this treatment option as well as those who work with these patients. The investigator was unable to locate any such qualitative studies within this body of research, suggesting it may be a unique and useful future contribution.

Conclusions

In conclusion, acceptable quality of life is achievable for long term survivors of CS+HIPEC. Individuals with a primary diagnosis of cancer of the appendix and with an R0/R1 resection status are likely to be over-represented among long-term survivors as

compared to those with alternate primary diagnoses or less optimal resection statuses. Among long-term survivors, physical health and functioning impairments are common, with overall physical quality of life significantly worse than that of the general population. Functioning in other domains, however, may not differ significantly or may be higher than that of the general population. Within this sample, overall Mental Health was significantly better than what is expected in the general population. Trends in quality of life scores demonstrated improvement over time, with significant improvement in Social Functioning from baseline to long-term follow-up. Additionally one third (31.70%) of participants reported significant sleep quality impairments. Sleep quality was related significantly to all quality of life domains, suggesting significant interrelations between sleep quality and all domains of functioning. The strongest relationship was found, not surprisingly, between sleep quality and Vitality. Finally, site of primary diagnosis had significant effects on the overall Physical Component scores of participants. Specifically, a primary diagnosis of cancer of the appendix was associated with significant positive contributions to long-term Physical Component scores.

Although one is able to draw from these findings with confidence, it is important to remain mindful of the inherent uniqueness of each patient's journey and survivorship trajectory. These data were provided by patients who lived to be long-term survivors and who were in satisfactory health to complete the questionnaires. The numerous individuals who were not alive at the time of the study or whose health impairments prevented them from participating were not represented. Mean scores should never overshadow the variability in experiences nor the continuing need to provide

interdisciplinary services, including attention to mental health and sleep quality, to those in need.

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APPENDIX A:
INSTRUCTIONS AND CONSENT FORMS

	Page
Telephone Transcript to Obtain Verbal Consent to Mail the Instruments and Consent Form.....	223
Consent to Act as a Human Participant (Wake Forest University Baptist Medical Center).....	225
Letter to prospective participants.....	230

**Phone script for CCCWFU 98597 protocol: Quality of Life Assessment for
Intraperitoneal Hyperthermic Chemotherapy Surgery Candidates**

"Hello, my name is _____. I am calling from Wake Forest University Baptist Medical Center to ask you to participate in a study of patients who have been treated with Cytoreductive Surgery + Intraperitoneal Hyperthermic Chemotherapy (CS plus IPHC). I am a member of our research and clinical team. As I understand it, you completed your IPHC treatment here. Is that correct?"

(wait for patient to respond and acknowledge; after patient acknowledges that he/she had his/her surgery here, proceed.)

"On behalf of your treatment team, I hope you are well. How are you feeling?"

(Listen to patients response and respond accordingly, offering empathy and encouragement as indicated)

A. If patient is currently enrolled in and within the 12 to 24 month time period of the QOL study (CCCWFU 98597):

"I also see that you are participating in our quality of life study following your treatment. We are interested in sending you an additional mailing of questionnaires to learn more about you and your life following this treatment. I would like to briefly explain the nature of this study. Is that OK?"

(wait for patient to respond; if patient acknowledges and is interested - continue)

B. If patient is not currently enrolled in ongoing QOL study or out more than 24 months from treatment, proceed with the following:

"I would like to explain to you the project that we are conducting in order to learn more about how people adapt and adjust after CS plus IPHC. May I briefly explain the nature of this study?"

(wait for patient to respond; if patient acknowledges and is interested - continue)

"We want to learn about the quality of life and adjustment of patients after treatment with CS + IPHC. If you agree to participate in this study, we will mail you a packet of questions related to your quality of life, sleep quality and treatment satisfaction. It will take approximately 15-20 minutes to complete these questions. We will ask you to complete these forms as accurately as possible and send them back to us in the self-addressed, postage-paid envelope provided within two weeks. There are no right or wrong answers to the questions you will be asked. We want to learn more about how people who have had this procedure do following treatment, and we hope to use this

information to improve our work with patients. For your time and contribution, we will send you a \$25 gas card when we receive your completed instruments. We may also call you to make sure you have received the questionnaire and to see if you have any questions."

"Do you have any questions about the study or anything I have said so far?" (*address questions*)

"Are you interested in participating in this study?" (*if yes, proceed; if no, thank them for their time*)

"May we send you this packet of instruments?" (*if person still agrees, explain the following:*)

"Enclosed in the packet, you will find a brief cover letter explaining the study, a consent form and the instruments. Please read the consent form and call us with any questions you may have prior to signing. Our contact information will be provided on the form. If you do not have any questions after reading through the information, please sign the consent form and complete the instruments. You may call us with any questions you have while completing the instruments. When finished, please send the consent form and packet back to us in the self-addressed, postage-paid envelope. When we receive this packet, we will then mail you the \$25 gas card."

"Do you have any more questions?" (*address questions*)

"Thank you for your time today and for your willingness to help with this study. We think your contributions will make a big difference in our understanding and counseling of patients before, during and after CS + IPHC. Thank you very much for your cooperation. If you would like to contact one of our study team, please call Katie Duckworth 336-713-6952/Adrienne Hill 336-713-6927.

Department of Internal Medicine, Hematology and Oncology

**QUALITY OF LIFE IN PATIENTS TREATED WITH INTRAPERITONEAL
HYPERTHERMIC CHEMOTHERAPY (IPHC) FOR PERITONEAL
CARCINOMATOSIS**

Richard P. McQuellon, Ph.D., Principal Investigator

INTRODUCTION

You are being asked to take part in a research study designed to learn more about how Intraperitoneal Hyperthermic Chemotherapy (IPHC) recipients manage the recovery and survivorship processes. This study will consist of the completion of one additional survey packet consisting of six questionnaires that will be mailed to your primary address. The questions within the survey will ask you to share information about your current quality of life, sleep quality and treatment satisfaction. Research studies are designed to gain scientific knowledge that may help other people in the future. You may ask your doctor or the study staff to explain any words or information that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn more about the quality of life, sleep quality and treatment satisfaction of cancer survivors one or more years following IPHC. This information may be useful to patients considering IPHC and will be used in future work with these patients.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 600 people who receive IPHC at Wake Forest University Baptist Medical Center will take part in a quality of life study. You are one of approximately 200 of these people that are being asked to complete an additional quality of life survey packet consisting of six questionnaires.

WHAT IS INVOLVED IN THE STUDY?

Previously enrolled subjects have completed questionnaires before their surgeries. This study will involve completing questionnaires at one time point after your surgery. You

will be asked to complete these questionnaires within a week of receiving them via the postal service and return them in the self-addressed, postage-paid envelope provided. These questionnaires include: (1,2) The Functional Assessment of Cancer Therapy and Treatment Satisfaction Scale (FACT-C; FACIT-TS); (3) the Medical Outcomes Study Short Form-36-Item Health Survey Questionnaire (SF-36); (4) the Pittsburgh Sleep Quality Index (PSQI); (5) an Informational Questionnaire; (6) and sociodemographic information. These questionnaires should take approximately 15-20 minutes to complete. A researcher will collect basic information from your medical chart on your cancer diagnosis, treatment, and history of previous medical conditions. Only the study staff will see this information.

HOW LONG WILL I BE IN THE STUDY?

You will be asked to complete one survey packet consisting of six questionnaires that you will receive at your home address via the mail. Study team members may call you to follow-up about 10 days after the questionnaire is mailed if: a.) you do not return the completed survey or b.) they would like to discuss some of your answers with you. After returning your completed packet, you are finished with this study.

WHAT ARE THE RISKS OF THE STUDY?

Participation in this study involves very little if any risk to you. You can discuss any risk of being in this study with the study staff. Some patients do report a heightened awareness of the psychological stresses involved with IPHC when reading the questionnaires and learning more about how quality of life is measured. If you do experience any feelings of anxiety or distress that are more than usual for you or what is common, our study staff and practitioners will talk with you and plan with you and your physician how to manage this.

Participating in this study may involve some information that you may consider confidential and private. This may make you feel uncomfortable and there is always the remote risk that this information may be accidentally released. However, efforts coding research records and keeping them secure so only study staff have access to them will be made to keep your information safe. We cannot guarantee absolute confidentiality and privacy although every effort will be made to do so.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You will receive no direct medical benefit by participation in this study. We hope the information learned from this study will benefit other people in the future. By taking part in this study, you will help increase scientific knowledge about the effects of IPHC on overall quality of life and survivorship.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is to not participate in this study.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. Any costs for your regular medical care which are not related to this study will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive a \$25 gas card upon completion of all questionnaires.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University Health Sciences. The researchers do not hold a direct financial interest in the sponsor.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential safety consequences. The investigators also have the right to stop your participation in the study at any time if it might be in your best medical interest.

WHAT ABOUT THE USE, DISCLOSURE AND CONFIDENTIALITY OF HEALTH INFORMATION?

By taking part in this research study, your personal health information, as well as information that directly identifies you, may be used and disclosed. Information that identifies you includes, but is not limited to, such things as your name, address, telephone number, and date of birth. Your personal health information includes all information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images, and information from study visits, phone calls, surveys, and physical examinations.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such

as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the institutional review board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study.

If this research study involves the treatment or diagnosis of a medical condition, then information collected or created as part of the study may be placed in your medical record and discussed with individuals caring for you who are not part of the study. This will help in providing you with appropriate medical care. In addition, all or part of your research related health information may be used or disclosed for treatment, payment, or healthcare operations purposes related to providing you with medical care.

When you sign this consent and authorization form you authorize or give permission for the use of your health information as described in the consent form. This authorization does not have an expiration date. You can revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address:

Richard P. McQuellon, Ph.D.

Wake Forest University Health Sciences

Department of Internal Medicine/ Hematology Oncology

Medical Center Boulevard

Winston-Salem, N.C. 27157

If you withdraw your authorization you will not be able to be in this study. If you withdraw your authorization, no new health information that identifies you will be gathered after that date. Your health information that has already been gathered may still

be used and disclosed to others. This would be done if it were necessary for the research to be reliable. You will not have access to your health information that is included in the research study records until the end of the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

Contact the study investigator, *DR. RICHARD MCQUELLON*, at (336) 716-7980.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, you should contact the Chairman of the IRB at (336) 716-4542.

You will be given a signed copy of this consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed)

Subject Signature

Date

Person Obtaining Consent

Date



Wake Forest University Baptist
MEDICAL CENTER®

Dear _____

We are writing to follow up on a phone conversation we had about the quality of life study we are conducting. A questionnaire is enclosed in this packet. This questionnaire is designed to help us learn about your overall quality of life, sleep quality, satisfaction with treatment, and other aspects of your functioning and well being following cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy (CS + IPHC). It will likely take you approximately 15-20 minutes to complete these instruments. As we mentioned in the phone conversation we will send you a \$25.00 gas card once we receive your completed questionnaires.

Please complete this questionnaire and the consent form within one week and return it in the enclosed self-addressed, postage-paid envelope. Your answers to these questions will help us understand more about how people adjust after CS + IPHC. Your contributions will make a big difference in our work here, especially in helping people understand the nature of this treatment.

If you have any questions, please contact Katie E. Duckworth at 336-713-6952 or Adrienne Hill at 336-716-6927.

Yours Sincerely,

Richard P. McQuellon, Ph.D.
Professor and Director, Psychosocial Oncology
and Cancer Patient Support Programs
336-716-7980

RPM/sll

APPENDIX B

PERMISSIONS AND INSTRUMENTS

	Page
Permission to Use the Medical Outcomes Study 36-Item Short-Form Health Survey	232
QualityMetric License Agreement for SF-36	234
Permission to Use QualityMetric SF-36 Scoring Software	236
Permission to Reprint SF-36 Instrument in Dissertation Appendix	237
Permission to Reproduce the Wilson and Cleary Model (1995)	238
Correspondence regarding the Wilson and Cleary Model (1995)	239
The Medical Outcomes Study 36-Item Short-Form Health Survey	240
The Pittsburgh Sleep Quality Index	246
Sociodemographic Questionnaire	250
Informational Questionnaire	253

From: Dana Kopec [dkopec@qualitymetric.com]
2:13 PM

Sent: Mon 8/10/2009

To: Katie Duckworth

CC:

Subject: QualityMetric University Order Form CT119211

Attachments: University Order Form.docx (56KB) University Disease-Specific ORDER FORM-01.09.docx (54KB)

Dear Katharine,

Thank you for completing our Survey Request Form. You qualify for the Office of Grants and Scholarly Research's (OGSR) Academic Research Licensing Program. The intent of the program is to provide our health survey tools royalty-free and offer scoring materials at discounted costs to the academic research community.

Please fill out the appropriate form with the survey(s) and scoring products you are interested in for your study. Once I receive the completed form back I will send you a formal quote.

If you are in financial need of a discount please let me know when returning the completed order form.

NO formatting or editing changes can be made to the survey: (Very Important - Please Read)

In order to obtain licensing from QualityMetric NO changes can be made to the survey forms.

Any format and/or language changes have the potential to affect the survey data received.

Therefore, to maintain the validation and integrity of the SF Health Surveys, **no language or formatting changes** are allowed. The format of the survey was scientifically engineered to facilitate accurate and unbiased data, as well as keeping the SF Health Survey in a visual format that is comprehensible to the patient/participant, including those who may be impaired and/or elderly. **You should administer the survey in the exact format you will receive it in. The only item the Licensee may add is a header with patient identification and / or administration information. If you do wish to add a header please ask for a sample copy of the survey to edit and then submit this to your account representative for review *prior to confirming a quote*.** Other than this, QualityMetric can not guarantee the validity and/or reliability of data obtained from using modified surveys and we will not be able to license any modified survey form. Once the licensing process is completed, you will receive a clean set of Survey Forms in a word and pdf. file. This is the form you will be administering. Please do not use any forms you may already have access to as the ones we send you are the most current versions.

Kind Regards,

Dana Kopec
Administrator-Office of Grants and Scholarly Research
QualityMetric Health Outcomes Solutions
24 Albion Road, Bldg. 400 | Lincoln, RI 02865
P: 401.642-9267 | F: 401.642.9356

From: navapi@qualitymetric.com [navapi@qualitymetric.com]
4:47 PM

Sent: Tue 10/6/2009

To: Katie Duckworth; eperrin@qualitymetric.com

CC:

Subject: Quality Metric Files

Attachments:

Dear Katharine Duckworth,

Below is a link to a compressed (zipped) archive file that contains your survey files.
Click on the link to download your file.

NOTE 1: Please verify that the survey forms, versions and languages that you receive are all correct. If there is any problem, contact your Qualitymetric representative immediately.

NOTE 2: If you receive Microsoft Word versions of the surveys, in addition to the Adobe Acrobat version, please print a hard copy of both the Adobe Acrobat and Microsoft Word files for each translation and compare them carefully before administering the surveys to your patients to verify that they are identical. Your computer may not have all the fonts installed to display and print the Microsoft Word document correctly. If you do not have Adobe Acrobat Reader installed on your computer, you can download a FREE copy at <http://www.adobe.com/support/downloads/main.html>.

File(s) will be available for download until **05 November 2009**:

Attachment: [QualityMetric-QM002117-20091006-164717.zip](#), 174.25 KB

You have received attachment link(s) within this email sent via Accellion Secure File Transfer. To retrieve the attachment(s), please click on the link(s).

[Accellion File Transfer](#)

From: Elisabeth Perrin [<mailto:eperrin@qualitymetric.com>]

Sent: Mon 8/24/2009 2:42 PM

To: Katie Duckworth

Subject: QualityMetric License Agreement #CT119211 OP002988

Dear Katie,

Thank you for your intent to license the QualityMetric health survey tools. Attached is your license agreement.

Follow the instructions below to execute the license agreement. Once we receive the signed license agreement, we will respond with a prepayment request. Once we receive payment we will complete your order.

Instructions:

1. Sign the first page of the license agreement.
2. Return the signed first page of the agreement by fax to me at 401-642-9356 or you may return a scanned copy via e-mail.

Note: It is not necessary to mail the signed licensed agreement if you fax it. A fax copy is considered a legal copy.

Cancellation: The licensee is obligated to follow the payment terms upon execution of the signed license agreement. We reserve the right to cancel the license agreement within 60 days from the date issued if we do not receive payment. If we cancel the license agreement, the licensee will be required to complete another license application if they wish to move forward. Please also note that there is no pricing guarantee; and current licensing fees will be applicable.

Changes to the license agreement: If there is updated information or incorrect data on the license agreement, please notify me in writing, and I will update the agreement. Please do not return the license agreement signed with any changes that have not been approved by QualityMetric Incorporated. Please note that changes to the license agreement will delay the processing of your license.

Kind Regards,

Elisabeth

Elisabeth Perrin

Administrative Assistant

Office of Grants and Scholarly Research (OGSR)

24 Albion Road, Bldg 400 | Lincoln, RI 02865

Phone: 401.334.8800 ext 256 | Fax: 401.642.9356

www.QualityMetric.com

NON-COMMERCIAL LICENSE AGREEMENT

Office of Grants and Scholarly Research (OGSR)

License Number: CT119211 / OP002988

Effective Date: August 24, 2009

Licensee Name: Wake Forest University

Licensee Address: Psychosocial Oncology Program
Katharine Duckworth
c/o Richard McQuellon
Medical Center Boulevard
Winston Salem, NC 27157-1082

Requested Administrations: 200 **Approved Administrations:** Two Times Requested
Administrations

Approved Use: Non-commercial academic research - unfunded – “Quality of Life Assessment for Intraperitoneal Hyperthermic Chemotherapy Surgery Candidates.”

Term: Beginning on October 1, 2009 and ending on September 30, 2012

Licensed Surveys: As indicated in Appendix B attached

Manuals: Licensee must purchase (or have purchased) from QM a copy of the manuals indicated in Appendix B attached

Royalty Fee: None, because this License is granted in support of the non-commercial
Approved Use below

Administrative Fee: \$450.00

Licensee accepts and agrees to the terms of this Non-Commercial License Agreement (the “Agreement”) from the Office of Scholarly Grants and Research (OGSR) of QualityMetric Incorporated (“QM”) as of the Effective Date.

Subject to the terms of this Agreement, including the QualityMetric Non-Commercial License Terms and Conditions attached as Appendix A: (a) QM grants to Licensee, and Licensee accepts, a non-exclusive, non-transferable, nonassignable, non-sublicensable worldwide license to use, solely for the Approved Use and during the License Term, the Licensed Surveys in the authorized Modes and Approved Languages indicated on Appendix B and to administer the Licensed Surveys only up to the Approved Administrations (and to make up to such number of exact reproductions of the Licensed Surveys necessary to support such administrations) in any combination of the specific Licensed Surveys and Approved Languages and Modes and to use any related software provided by QM and (b) Licensee agrees to pay the Administrative Fee and other applicable charges in accordance with the attached invoice. Capitalized terms used in this Agreement and not otherwise defined herein shall have the meanings assigned to them in Appendix A. The appendices attached hereto are incorporated into and made a part of this Agreement for all purposes.

Wake Forest University
Psychosocial Oncology Program
Katharine Duckworth
c/o Richard McQuellon
Medical Center Boulevard
Winston Salem, NC 27157-1082

Signature: _____

Name: _____

Title: _____

For additional information about QM's OGSR , go to <http://www.qualitymetric.com/advancing/>

From: Elisabeth Perrin leperrin@qualitymetric.com
11:49 AM

Sent: Wed 10/28/2009

To: Katie Duckworth

Subject: Your QualityMetric Health Outcomes Scoring Software 2.0 Activation Key

Attachments: Installation GuideV2.pdf(822KB)

Dear Katharine Duckworth

Thank you for purchasing the QualityMetric Health Outcomes(TM) Scoring Software 2.0. Enclosed in this email is the Activation Key you will need to enter in order to enable functionality in your software. The details of your purchase are as follows:

Product Version: Health Outcomes SS 2.0 - 1 year

Purchase Date: 10/16/09

SF-8 Survey License Count: 0

SF-10 Survey License Count: 0

SF-12 Survey License Count: 0

SF-12v2 Survey License Count: 0

SF-36 Survey License Count: 0

SF-36v2 Survey License Count: 0

Activation Key(s):

EBD1A-EDCB9-F285C-BD7C6

You may download the QualityMetric Health Outcomes Scoring software at the following location:

<http://www.qualitymetric.com/download/SFScoringSoftwareV2Setup.exe>

Please save and/or print this message. In order to register and install your Activation Key your computer will need an active Internet connection. Please refer to the attached installation document if you require a detailed instructions.

Attached to this email message you will also find a copy of the Installation Instructions for the QualityMetric QualityMetric Health Outcomes(TM) Scoring Software 2.0. The attached file is in .pdf format and requires that you have Adobe Acrobat Reader installed on your computer. You may download Acrobat Reader for free at www.adobe.com. If you have any questions or concerns, please feel free to contact us at webmaster@qualitymetric.com.



QualityMetric.com

December 11, 2009

Katie Duckworth
309 Pisgah Church Rd, Apt 3H
Greensboro, NC 27455

Email: Kduckwor@wfubmc.edu
Phone: 336-713-6952

Dear Katie:

In response to your request, I am pleased to provide you with approval of nonexclusive world rights to reproduce the SF-36® Scales Measure Physical and Mental Components of Health Figure in its original format from the *SF-36™ Physical and Mental Health Summary Scales: A User's Manual..* This information shall be reproduced solely for the purpose of your publication entitled <http://www.sf-io.org/tools/sf36.shtml>.

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In addition, any reference to the guide and survey form(s) should be cited as follows:

Ware JE, Kosinski M, Keller SK. *SF-36™ Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: The Health Institute, 1994.

Sincerely,

A handwritten signature in black ink, appearing to read 'James Nemiah', is written over a horizontal line.

James Nemiah
CEO & Chief Legal Counsel

JN/DK

Wednesday, November 11, 2009

Permission Granted Notification

Client Number: 15558

Request Number: 25015

Katie Duckworth

The University of North Carolina at Greensboro
Dept of Counseling & Educational Development
228 Curry Building -PO Box 26170
Greensboro, NC 27402-6170 USA

In response to your request to use:

Journal Item	Citation	Year	Specific
Journal of the American Medical Association	273(1):59-65	1995	Figure

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Correspondence regarding the Wilson and Cleary Model (1995):

From: Katie Duckworth [mailto:kduckwor@wfubmc.edu]
Sent: Tue 11/10/2009 3:45 PM
To: Wilson, Ira
Subject: permission to reproduce model

Dr. Wilson,
Hello, my name is Katie Duckworth. I am a part-time employee within the Cancer Patient Support/Psychosocial Oncology Programs here at Wake Forest University Baptist Medical Center and am also a doctoral student in the middle of dissertation. In my dissertation, I am examining the QOL and sleep quality of long term survivors of peritoneal metastases from a variety of primary origins who were treated here with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS+HIPEC). I am referencing/incorporating your HRQOL model within my dissertation and am requesting permission to reproduce a diagram of the model within the text as well. I want to thank you in advance for your consideration of this request.

Sincerely,
Katie Duckworth

Katie E. Duckworth, MA
Doctoral intern
Psychosocial Oncology & Cancer Patient Support Program
Wake Forest University Baptist Medical Center
kduckwor@wfubmc.edu
pager: 806-6682
office: 336-713-6952

From: Wilson, Ira [mailto:IWilson@tuftsmedicalcenter.org]
Sent: Tuesday, November 10, 2009 7:28 PM
To: Katie Duckworth
Cc: Cleary, Paul
Subject: RE: permission to reproduce model
Katie,
It is fine with me, but you have to ask Jama, since they own the copyright.
Ira Wilson

From: Cleary, Paul [paul.cleary@yale.edu]
Sent: Tue 11/10/2009 8:16 PM
To: Wilson, Ira; Katie Duckworth
Cc:
Subject: RE: permission to reproduce model

Ditto. Good luck with your dissertation!






Paul

Your Health and Well-Being






This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☐ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
				
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
				
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

SF-36v2™ Scales Measure Physical and Mental Components of Health 1994, by The Health Institute – All rights reserved
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3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
a <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
b <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
c Lifting or carrying groceries	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
d Climbing <u>several</u> flights of stairs	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
e Climbing <u>one</u> flight of stairs.....	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
f Bending, kneeling, or stooping.....	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
g Walking <u>more than a mile</u>	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
h Walking <u>several blocks</u>	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
i Walking <u>one block</u>	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃
j Bathing or dressing yourself	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Yes	No
▼	▼

- a Cut down on the amount of time you spent on work or other activities ☐₁ ☐₂
- b Accomplished less than you would like ☐₁ ☐₂
- c Were limited in the kind of work or other activities ☐₁ ☐₂
- d Had difficulty performing the work or other activities (for example, it took extra effort) ☐₁ ☐₂

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Yes	No
▼	▼

- a Cut down on the amount of time you spent on work or other activities ☐₁ ☐₂
- b Accomplished less than you would like ☐₁ ☐₂
- c Did work or other activities less carefully than usual ☐₁ ☐₂

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼	▼

- a Did you feel full of pep? ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- b Have you been a very nervous person? ... ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- c Have you felt so down in the dumps that nothing could cheer you up? ... ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- d Have you felt calm and peaceful? ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- e Did you have a lot of energy? ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- f Have you felt downhearted and blue? ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- g Did you feel worn out? ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- h Have you been a happy person?..... ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆
- i Did you feel tired? ☐₁ ☐₂ ☐₃ ☐₄ ☐₅ ☐₆

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a I seem to get sick a little easier than other people.....	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
b I am as healthy as anybody I know	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
c I expect my health to get worse	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅
d My health is excellent	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

Thank you for completing these questions!

Subject's Initials_____ ID# _____ Date_____ Time _____AM/PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you .

- a) Cannot get to sleep within 30 minutes

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

- b) Wake up in the middle of the night or early morning

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

- c) Have to get up to use the bathroom

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

d) Cannot breathe comfortably

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

e) Cough or snore loudly

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

f) Feel too cold

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

g) Feel too hot

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

h) Had bad dreams

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

i) Have pain

Not during the past month _____ Less than once a week _____ Once or twice a week _____ Three or more times a week _____

j) Other reason(s), please

describe _____

How often during the past month have you had trouble sleeping because of this?

Not during the	Less than	Once or twice	Three or more
past month _____	once a week _____	a week _____	times a week _____

6. During the past month, how would you rate your sleep quality overall?

Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all	_____
Only a very slight problem	_____
Somewhat of a problem	_____
A very big problem	_____

10. Do you have a bed partner or room mate?

No bed partner or room mate	_____
Partner/room mate in other room	_____
Partner in same room, but not same bed	_____
Partner in same bed	_____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

c) Legs twitching or jerking while you sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

d) Episodes of disorientation or confusion during sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

e) Other restlessness while you sleep; please describe

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

**QUALITY OF LIFE IN PATIENTS TREATED WITH INTRAPERITONEAL
HYPERTHERMIC CHEMOTHERAPY (IPHC) FOR PERITONEAL
CARCINOMATOSIS**
CCCWFU 98597

SOCIODEMOGRAPHIC DATA SHEET

ID #

Patient's Name _____ Date _____

Address _____ Gender ____ Female ____ Male

Phone _____

Diagnosis _____ Date of Diagnosis _____

Physician _____

Age _____ Date of Birth _____

1.a. What is your ethnicity: (Check One)

____(H) Hispanic

____(N) Non-Hispanic

1.b. What is your race? (Check all that apply)

____(W) White

____(A) Asian ____ (P) Pacific Islander/Hawaiian

____(B) Black

____(NA) Native American

2. What is your marital status? (Check one)

____(1) Single

____(4) Divorced

____(2) Married

____(5) Widowed

____(3) Separated

3. With whom do you live? (Check All That Apply)

____(1) Wife/Husband

____(5) Parent(s) Parent in law

____(2) Girlfriend/Boyfriend

____(6) Others (specify, __)

____(3) Live Alone

____(4) Children (Ages: ____ / ____ / ____ / ____)

4. What is the highest grade you finished in school? (Check One)

____(1) 1-8 grades ____ (5) Junior College Degree

____(2) 9-11 grades ____ (6) College Degree (BA./B.S.)

____(3) High school grad ____ (7) Some Post-College Work

____(4) Some college ____ (8) Advanced Degree

5. What is your current employment status? (Check One)

- ____(1) Homemaker
- ____(2) Disabled (Usual Occupation_____)
- ____(3) Unemployed
- ____(4) Retired
- ____(5) Currently working full-time
- ____(6) Currently working part-time
- ____(7) Student

6. A. What is your occupation?_____

B. What is your spouse's occupation?_____

7. What is your annual family income? (Check One)

- | | |
|-----------------------|-------------------------|
| ____(1) 0-4,999 | ____(6) 40,000-49,999 |
| ____(2) 5,000-9,999 | ____(7) 50,000-59,999 |
| ____(3) 10,000-19,999 | ____(8) 60,000-69,999 |
| ____(4) 20,000-29,999 | ____(9) 70,000 and over |
| ____(5) 30,000-39,999 | |

8. What type of health insurance do you have? (Check All That Apply)

- | | |
|--|-----------------------------------|
| ____(1) Medicaid | ____(6) Individual Hlth Insurance |
| ____(2) Medicare Only | ____(7) Group Health Insurance |
| ____(3) Medicare + Supplemental | ____(8) V.A./Military |
| ____(4) Disability Insurance | ____(9) No Insurance |
| ____(5) HMO (Partners, QualChoice, etc.) | ____(10) Other, Specify_____ |

INFORMATION ABOUT YOUR ILLNESS

What are the 3 or 4 most troubling symptoms or problems that you now have? Rate the severity of each on a 1-10 scale, with 1 being very mild and 10 being as severe as you could imagine.

SYMPTOM/PROBLEM

1-10 RATING

Are you currently receiving any treatments?

YES _____ NO ____

If Yes, what are the treatments? _____

Physician: _____

Date of your most recent treatment: _____

WHO Performance Scale

Performance Status-Patient Rated

Circle the number that best describes your current activity level:

- 0 I have normal activity
- 1 I have some symptoms, but I can walk and I do not spend any extra time in bed
- 2 I need some time in bed, but it is less than 50 % of normal daytime
- 3 I need to be in bed greater than 50 % of normal daytime
- 4 I am unable to get out of bed

Additional Questions CCCWFU 98597

Cytoreductive Surgery (CS) + Intraperitoneal Hyperthermic Chemotherapy (IPHC)

Part I: Please circle the number that best indicates how much you agree with the statements below.

1.) I regret my decision to undergo this surgery + heated chemotherapy (IPHC).

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

2.) My sleep quality prior to surgery + heated chemotherapy (IPHC) was poor.

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

3.) Before learning about surgery + heated chemotherapy (IPHC), I was told by my doctors that there was nothing more I could do for treatment.

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

4.) After surgery + heated chemotherapy (IPHC) I was given good information and counseling about how to return to **normal eating**.

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

6.) After surgery + heated chemotherapy (IPHC) I was given good information and counseling about how to return to **normal activity**.

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

7) After surgery + heated chemotherapy (IPHC) I was given good information and counseling about **exercise and physical rehabilitation**.

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

8) After surgery + heated chemotherapy (IPHC) I was given good information and counseling about my **emotional reaction to the treatment and hospitalization**.

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

Part II

Please circle the answer (yes or no) that applies to you.

- 1.) Additional treatment options were given to me at the time I chose surgery and heated chemotherapy (IPHC). Yes No
- 2.) Before I had surgery + heated chemotherapy (IPHC) I was told all that I needed to know about what to expect. Yes No
- 3.) After surgery + heated chemotherapy (IPHC) I talked to a nutritionist about my diet. Yes No
- 4.) After surgery + heated chemotherapy (IPHC) I talked to a physical therapist about exercising to help my recovery. Yes No
- 5.) After surgery + heated chemotherapy (IPHC) I talked to a counselor about my emotional reactions to treatment. Yes No

Part III

Please answer the questions below. If you need more space, use the back of this questionnaire.

- 1.) Were you ever told by your medical team that you had only a certain amount of time to live due to the nature of your diagnosis? What was said?

- 2.) From hospitalization through follow-up care, what has been the most difficult aspect of your surgery + heated chemotherapy (IPHC) experience?

- 3.) Could anything have been done to improve the quality of your experience?

4.) What information would you give to someone considering having this surgery + heated chemotherapy (IPHC)?

5.) Please list other family members who were previously diagnosed with cancer. What were their diagnoses?

Please make any additional comments that could help us improve patient care:

Thank You for your help

APPENDIX C:

PILOT STUDY METHODS AND RESULTS

	Page
Pilot Study.....	258
Research Questions and Hypotheses	258
Participants.....	259
Instrumentation	260
Procedures.....	260
Data Analysis and Overview of Results	261
Table A: Sociodemographic Description of the Pilot Study Sample.....	266
Table B: Means and Medians of SF-36 Subscales.....	267
Figure A: Norm-based Subscale Scores of Pilot Sample.....	267
Table C: Norm-based Physical Component Scores of the SF-36.....	268
Figure B: Norm-based Physical Component Scores.....	268
Table D: Norm-based Mental Component Scores of the SF-36.....	269
Figure C: Norm-based Mental Component Scores.....	269
Table E: Pearson Correlation Coefficients, SF-36 Subscales	270
Table F: Scale Reliability and Homogeneity Estimates	270
Table G: Change at follow-up: PF, RP, and BP	270
Table H: PSQI Global and Subscale Scores	271
Table I: PSQI Global Score Mean Comparisons	271
Table J: PSQI Clinical Cut-off >8	272

Table K: Correlations: QOL Subscale Scores and Global Sleep Quality Scores	272
Table L: Means by Resection Status.....	273

Pilot Study

Research Questions and Hypotheses

This pilot study was conducted to field test the procedural aspects of the investigation as well as the instrumentation and corresponding instructions. Similarly, in order to test data analysis procedures for each of the research questions established for the full study, the pilot data was analyzed accordingly. Although the pilot sample is of an insufficient size from which to draw conclusions, the preliminary results are listed below.

Research Question 1: What are the QOL subscale scores (i.e. Physical Functioning, Role Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health, Reported Health Transition) of participants, as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) instrument, and how do they compare to those of general population norms?

Hypothesis 1a: The QOL subscale scores of participants will be lower than the standardized population norms.

Research Question 2: Regarding those participants for whom pre-surgical data is available, what differences exist between pre-surgical QOL subscale scores and 12 or more-month QOL scores for participants who received CS+HIPEC and have survived?

Hypothesis 2a: Post-surgical, 12-month Physical Functioning (PF), Role Physical (RP) and Bodily Pain (BP) subscale scores will be significantly higher than those acquired from Participants pre-surgery.

Research Question 3: What is the sleep quality of participants, as defined by one's global and component scores on the Pittsburgh Sleep Quality Index (PSQI)?

Hypothesis 3a: Global PSQI scores of the majority of CS+HIPEC patients will be above the recommended clinical threshold of eight, indicating poor sleep quality.

Research Question 4: What relationship exists between sleep quality and QOL subscale scores?

Hypothesis 4a: A significant positive relationship will exist between global sleep quality scores and the QOL subscale scores.

Research Question 5: What are the respective contributions of age at CS+HIPEC and resection status (RO/R1, R2a, R2b, and R2c) in predicting QOL subscale scores at 12 or more months in participants with varying primary tumor sites?

Hypothesis 5a: Patients who achieved a better resection status will demonstrate higher QOL scores at 12 or more months.

Hypothesis 5b: Patients with appendiceal tumors and pseudomyxoma peritonei will demonstrate higher QOL scores at 12 or more months.

Participants

The names of approximately ten percent (n=19) of the potential full-study participants were selected at random from the master database containing the names of all CS+HIPEC recipients from Wake Forest University Baptist Medical Center. Of these 19 individuals, telephone contact was made with 17, and all 17 gave verbal consent to participate and have the survey mailed to their home address. Within ten days time, 13 individuals (76.47% of the 17 individuals who were contacted) returned the completed instruments. If all potential participants, including those not contacted via telephone within the window of pilot study time, are included (i.e. 13/19), the overall response rate

was 68.42%. This response rate was surprisingly large given the nature of survey research and the characteristics of the sample. It is important to note that one participant returned the completed survey following the end of the pilot study timeframe, suggesting the potential need to extend the data collection window. Also, one of the 17 individuals who gave verbal consent to participate called following the reception of the packet to verbalize that she was too ill and deconditioned to complete the survey. She returned the survey without providing any data. In conclusion, the pilot data presented here were provided by 13 individuals who had CS+HIPEC at Wake Forest University Baptist Medical Center at least 12 months prior to the pilot study date. Further demographic information is found in Table 2.

Instrumentation

After giving verbal consent to participate over the telephone, prospective participants were sent a cover letter, a long form consent, the battery of instruments (including the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), the Pittsburgh Sleep Quality Index (PSQI), a Sociodemographic Questionnaire, and a Patient Information Questionnaire), and a self-addressed, postage-paid envelope. Also, in the initial phone interview, patients were asked to indicate on the packet if the process required an excess of 20 minutes or if any particular items were confusing.

Procedures

In this order, requests to complete this study were submitted to and approved by the Human Subjects Review Board at Wake Forest University Baptist Medical Center followed by that of The University of North Carolina at Greensboro. Following

notification of approval from the Board at the second institution, packets were prepped for mailing, and prospective participants' names were randomly selected from the hospital master database containing names of all individuals who have had CS+HIPEC at WFUBMC. Calls to secure verbal consent were made over a period of one week's time, and packets were mailed the day that verbal consent to participate was secured from a respective individual. A total of ten days were allocated for data collection. As packets were received, they were perused for any missing data, and data were entered into secure databases created by the investigator. Responses to single missing items were acquired over the telephone. Finally, within a two week time period from when the completed packet was received by the investigator, each participant was sent a letter of gratitude for her or his participation, a copy of her or his signed consent form, and a \$25 gift card to Shell gas stations.

Data analysis and Overview of Results

Frequencies were computed for the demographic questions and are presented in Table A. Results for the hypotheses are outlined below.

Hypothesis 1a. To answer hypothesis 1a, descriptive statistics were calculated for each of the eight QOL subscale scores as well as the overall mental and physical component scores (MCS, PCS; see results in Tables B-D). The SF-36 scoring software utilizes norm-based scoring that relies on a linear T-score transformation with a mean of 50 and standard deviation of 10 (Ware, n.d.). Upon comparing the mean scores on the two higher-ordered clusters (i.e. MCS and PCS), it is apparent that, collectively, the pilot participants are faring better mentally (MCS mean = 51.6, SD = 10.9) than physically

(PCS mean = 44.2, SD = 12.1). Given the diagnostic and treatment history of these individuals, the lower PCS scores are not surprising. Within the PCS, the lowest mean subscale score was on RP (mean = 43.2, SD = 13.8), followed by PF (mean = 45.2, SD = 11.1). Surprisingly, the mean MCS of these pilot participants is above that which might be anticipated for a person in the general population (mean of 50). However, for each of the subscale scores, it is important to note the range of scores in addition to the mean or median scores. The presence of outlier scores that are approximately two to three standard deviations below the mean on most subscales suggests that some of these survivors are reporting significant emotional and physical suffering while others are not. Although it is not possible to make any generalizations based on such a small sample, it will be important to consider variability of scores among the full study sample.

Additionally, Cronbach's alpha (see Table F) ranged from 0.794 (RE) to 0.961 (RP), suggesting acceptable evidence of internal consistency with this sample. Pearson Product Moment Correlation coefficients also were calculated between each of the subscales, and the results are located in Table 6. With the exception of correlations between the GH and RE subscales and the MH and PF subscales, all subscales were correlated significantly. Finally, some items demonstrated poor discriminant validity with this small pilot sample, correlating significantly higher with alternate scales than with their hypothesized scales (e.g. GH02= 0.39 with GH versus 0.61 with SF).

Hypothesis 2a. To test hypothesis 2a, a paired t-test was performed (see Table G) to examine differences in mean baseline and 12 or more month follow-up PF, RF, and BP subscale scores in the subset of participants for whom baseline data were available ($n =$

9). No significant differences were found, presumably due to the small sample size.

Although the findings were not statistically significant, it is interesting to note that the mean change scores for PF (-2.1), RP (-2.4), and BP (-6.7) were all negative, indicating worse physical functioning and physical role functioning as well as increased bodily pain at the follow-up measurement as compared to the baseline measurement. These findings are contrary to what was hypothesized and may simply be an artifact of the small sample.

Hypothesis 3a. To answer hypothesis 3a, descriptive statistics were calculated in order to acquire the mean subscale and overall PSQI scores (see Table H). The mean overall PSQI score for pilot participants was 9.2 (SD 5.0), which is above eight, the more conservative cutoff point selected for this study. Only 38.46% of this pilot sample scored below the recommended cutoff of eight, suggesting roughly 61% of these individuals currently report poor sleep quality (see Table J). Likewise, this overall score of 9.2 is well above the mean score found for individuals without sleep-related concerns (mean = 2.67, SD 1.70) in the Buysse et al. (1989) study. The highest mean subscale scores (high scores indicate worse sleep quality) were on the sleep latency (mean = 1.7, SD = 1.0) and sleep disturbance (mean = 1.7, SD = 0.9) subscales. It takes these pilot participants an average of 34.6 minutes to fall asleep, and the most common sleep disturbances include, in this order, bathroom-related awakenings, middle-of-the-night or early morning awakenings, poor sleep latency, pain, and the sensation of being too cold.

Hypothesis 4a. To answer hypothesis 4a, Pearson correlation coefficients were calculated to determine the relationship that exists between global sleep quality scores and the QOL subscale scores (see Table K). Given that a *lower* QOL subscale score

indicates poorer QOL, while a *higher* PSQI score indicates poorer sleep quality, a negative correlation between the two variables actually signifies that these variables move together (i.e. a positive relationship). Significant negative correlations were found between overall PSQI scores and PF ($-0.647, p = 0.017$), RP ($-0.700, p = 0.008$), GH ($-0.837, p = 0.000$), VT ($-0.774, p = 0.002$), and PCS ($-0.761, p = 0.003$), suggesting positive relationships between sleep quality and the aforementioned QOL subscale and component scores. For example, as the PF subscale score went down (indicating worse physical functioning), the PSQI score went up (indicating worse sleep quality). In summary, the hypothesis that significant positive relationships between overall PSQI scores and QOL subscale scores was met relative to physical functioning, role physical, general health, vitality, and the overall physical component score.

Hypothesis 5a. Finally, insufficient data was obtained in the pilot study to answer research question five. Specifically, due to the scarcity of data for some cells needed in the model (i.e. tumor site and resection status), the ANOVA was not run. However, an examination of the QOL means when divided by resection status demonstrates some noteworthy trends (see Table L) that appear to support hypothesis 5a. For example, the mean PF scores for those with a resection status of R0/1 ($n = 10$) versus R2a ($n = 1$) versus R2b ($n = 2$) were 48 (SD = 8.9), 36.2, and 32.0 (SD = 14.8), respectively. Similar trends are noted across other subscales. Results of the Kruskal-Wallis Test support the existence of significant differences between the three groups (i.e. R0/1, R2a, and R2b) relative to VT ($p = 0.038$), SF ($p = 0.034$), and RE ($p = 0.038$). Although a regression model to gauge the respective contributions of resection status and

tumor site to QOL was not run, these initial findings suggest that QOL differences may exist between those with varying resection statuses.

Hypothesis 5b. Again, hypothesis 5b was not tested given the characteristics of the pilot sample. Within the sample, seven individuals had a primary diagnosis of appendiceal cancer, two had a primary diagnosis of colon cancer, and the remaining individuals had a primary cancer diagnosis of liver, mesothelioma, sarcoma, or “other”. It is noteworthy that over 50% of the pilot sample had a primary diagnosis of appendiceal cancer, potentially suggesting that those with carcinomatosis of appendiceal origin may be better represented among the long-term survivors (i.e. they might have longer life expectancies post-CS+HIPEC).

Table A

Sociodemographic Description of the Pilot Study Sample (N = 13)

Variable	Mean	Median	Range	n
Age	60.15		32-81	13
Age at CS+HIPEC	54.46		31-77	13
CS+HIPEC Date		8/2005	5/1993-9/2008	13
Gender				
Female				8
Male				5
Race				
Black				1
White				12
Ethnicity				
Hispanic				1
Non-Hispanic				12
ECOG Performance Status				
0				7
1				6
Resection Status				
R0/1				10
R2a				1
R2b				2
State of Residence				
FL				1
NC				9
NJ				1
SC				1
VA				1
Diagnoses				
Appendix				7
Colon				2
Liver				1
Mesothelioma				1
Sarcoma				1
Other				1

Table B
Means and Medians of SF-36 Subscales

Variable	N	Mean	Std Dev	Median	Minimum	Maximum
PF_NBS	13	45.2	11.1	44.6	21.5	57.1
RP_NBS	13	43.2	13.8	49.2	28.0	56.2
BP_NBS	13	49.7	11.7	46.5	33.2	62.8
GH_NBS	13	45.3	13.1	43.9	26.5	64.0
VT_NBS	13	47.6	13.1	44.3	32.5	70.4
SF_NBS	13	50.5	10.2	57.1	24.6	57.1
RE_NBS	13	48.9	11.0	55.3	23.7	55.3
MH_NBS	13	51.0	12.2	50.4	25.5	64.1
PCS_NBS	13	44.2	12.1	41.3	27.9	59.2
MCS_NBS	13	51.6	10.9	53.9	30.7	64.7

Figure A. Norm-based Subscale Scores of Pilot Sample

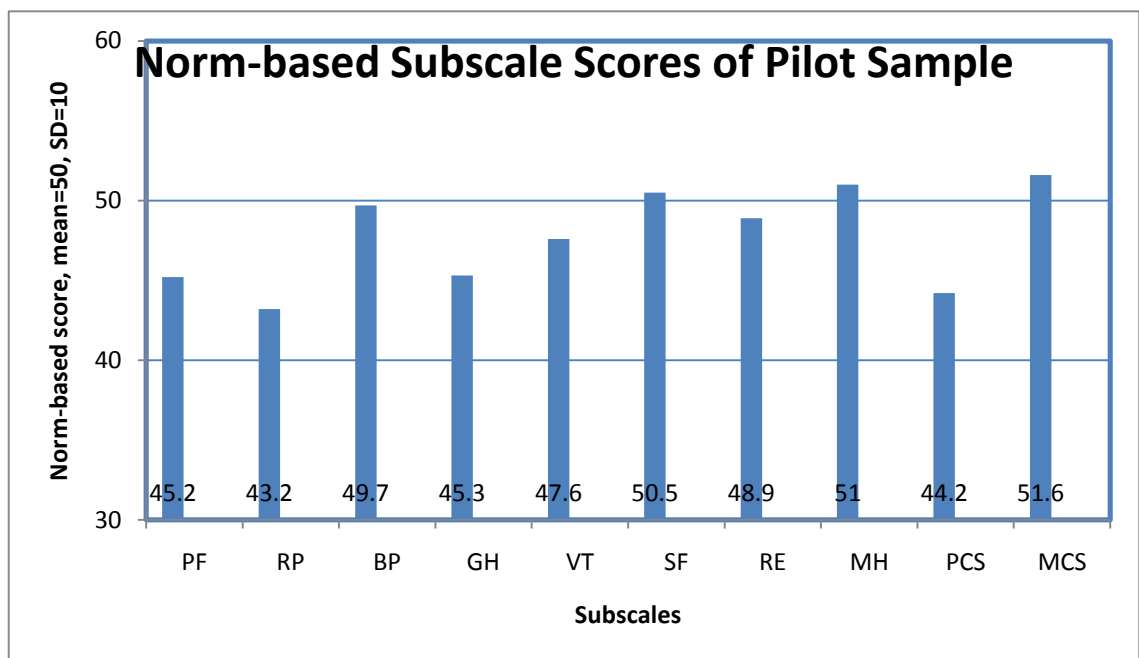


Table C

Norm-based Physical Component Scores of the SF-36

PCS-NBS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
27.87	1	7.69	1	7.69
28.29	1	7.69	2	15.38
30.39	1	7.69	3	23.08
33.54	1	7.69	4	30.77
37.24	1	7.69	5	38.46
40.69	1	7.69	6	46.15
41.25	1	7.69	7	53.85
51.77	1	7.69	8	61.54
54.99	1	7.69	9	69.23
55.90	1	7.69	10	76.92
56.07	1	7.69	11	84.62
58.00	1	7.69	12	92.31
59.16	1	7.69	13	100.00

Figure B. Norm-based Physical Component Scores

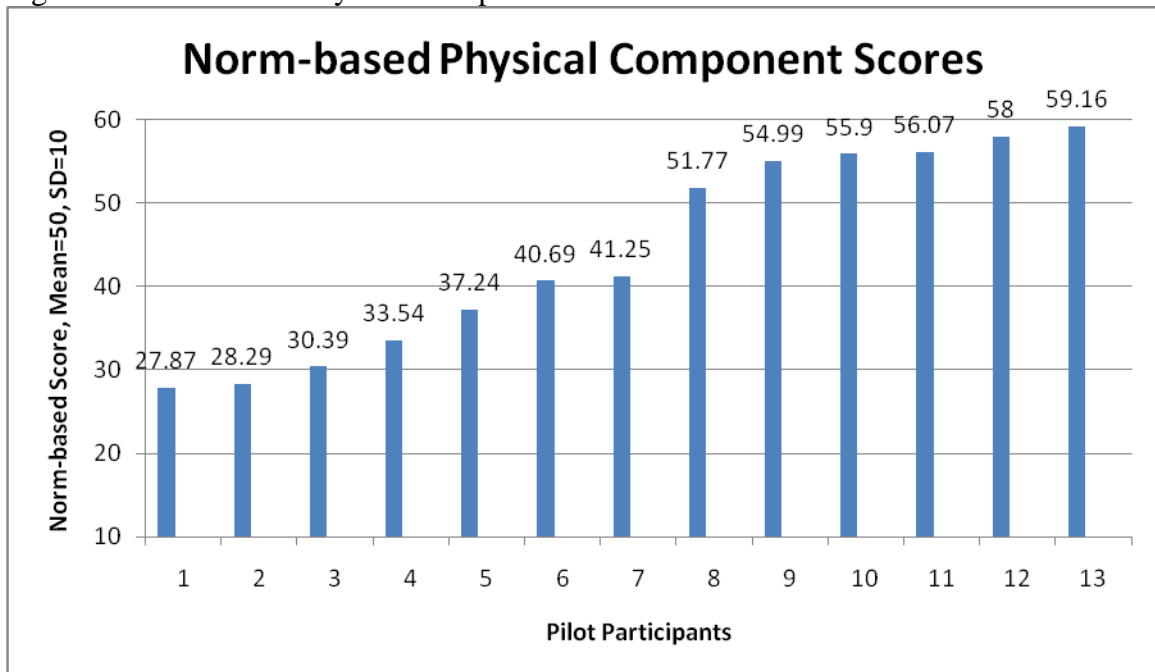


Table D

Norm-based Mental Component Scores of the SF-36

PCS-NBS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
30.71	1	7.69	1	7.69
31.34	1	7.69	2	15.38
41.91	1	7.69	3	23.08
48.36	1	7.69	4	30.77
51.60	1	7.69	5	38.46
53.40	1	7.69	6	46.15
53.86	1	7.69	7	53.85
54.02	1	7.69	8	61.54
58.02	1	7.69	9	69.23
60.25	1	7.69	10	76.92
60.38	1	7.69	11	84.62
61.99	1	7.69	12	92.31
64.67	1	7.69	13	100.00

Figure C. Norm-based Mental Component Scores

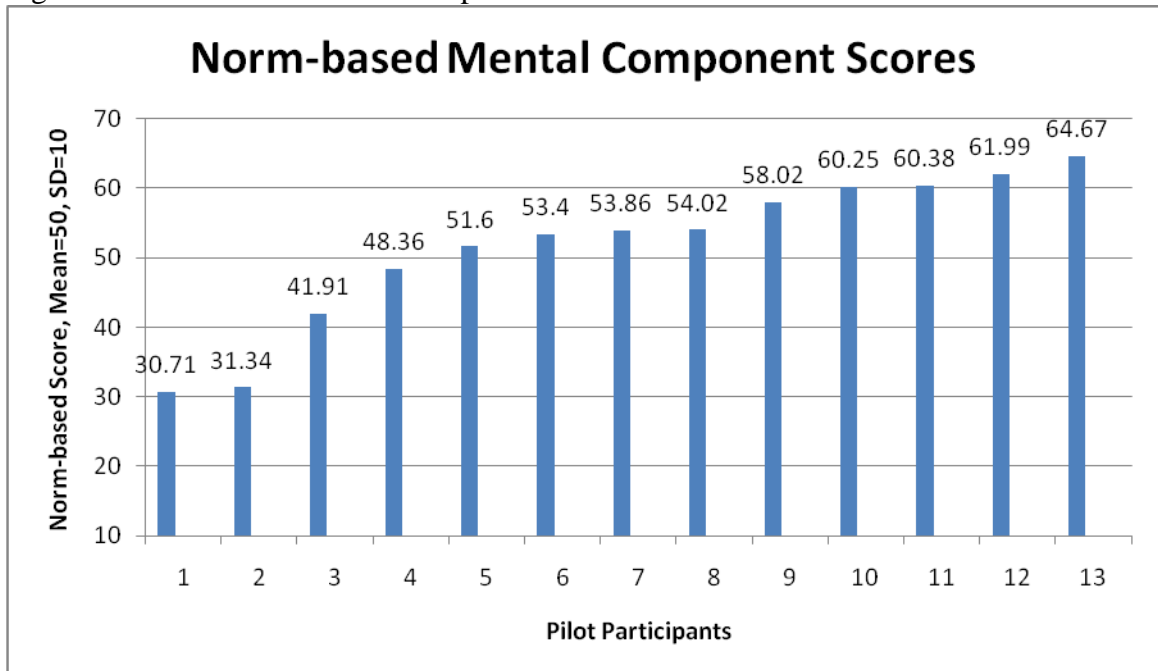


Table E

Pearson Correlation Coefficients, SF-36 Subscales, N=13

	PF_NBS	RP_NBS	BP_NBS	GH_NBS	VT_NBS	SF_NBS	RE_NBS	MH_NBS
PF_NBS	1.000	0.871 0.0001	0.701 0.0076	0.727 0.0049	0.869 0.0001	0.701 0.0076	0.743 0.0036	0.546 0.0534
RP_NBS	0.871 0.0001	1.000	0.748 0.0033	0.766 0.0023	0.898 <.0001	0.579 0.0381	0.664 0.0133	0.608 0.0273
BP_NBS	0.701 0.0076	0.748 0.0033	1.000	0.586 0.0354	0.813 0.0007	0.662 0.0137	0.688 0.0093	0.813 0.0007
GH_NBS	0.727 0.0049	0.766 0.0023	0.586 0.0354	1.000	0.830 0.0004	0.616 0.0249	0.500 0.0820	0.651 0.0159
VT_NBS	0.869 0.0001	0.898 <.0001	0.813 0.0007	0.830 0.0004	1.000	0.683 0.0100	0.660 0.0131	0.762 0.024
SF_NBS	0.701 0.0076	0.579 0.0381	0.662 0.0137	0.616 0.0249	0.683 0.0100	1.000	0.730 0.0047	0.774 0.0019
RE_NBS	0.743 0.0036	0.664 0.0133	0.688 0.0093	0.500 0.0820	0.660 0.0131	0.730 0.0047	1.000	0.770 0.0021
MH_NBS	0.546 0.0534	0.608 0.0273	0.813 0.0007	0.651 0.0159	0.762 0.024	0.774 0.0019	0.770 0.0021	1.000

Table F

Scale Reliability and Homogeneity Estimates

Scale	Number of Items	Cronbach's Alpha	Average Inter-item Correlation
PF	10	0.932	0.580
RP	4	0.961	0.859
BP	2	0.953	0.911
GH	5	0.851	0.534
VT	4	0.951	0.829
SF	2	0.865	0.763
RE	3	0.794	0.563
MH	5	0.822	0.481

Table G

Change at follow-up: PF, RP, and BP

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	p-value
PF	9	-2.1	7.3	-2.1	-14.1	8.4	0.4119
RP	9	-2.4	10.0	0.0	-28.3	7.1	0.4998
BP	9	-6.7	10.9	-9.0	-25.3	12.0	.1043

Table H

Pittsburgh Sleep Quality Index Global and Subscale Scores

Subscale	N	Mean	Std Dev	Minimum	Maximum
Sleep Quality	13	1.3	0.9	0.0	3.0
Sleep Latency <i>Minutes to Fall Asleep:</i>	13	1.7 34.6	1.0	0.0 5	3.0 90
Sleep Duration	13	1.2	1.0	0.0	3.0
Habitual Sleep Efficiency	13	1.3	1.3	0.0	3.0
Sleep Disturbance	13	1.7	0.9	0.0	3.0
Use of Sleep Medication	13	1.4	1.6	0.0	3.0
Daytime Dysfunction	13	0.7	0.6	0.0	2.0
Total PSQI	13	9.2	5.0	1.0	16.0

Table I

Pittsburgh Sleep Quality Index Global Score Mean Comparisons

Group	N	Mean PSQI Global Score	Std Dev
CS+HIPEC Survivors*	13	9.2	5.0
Controls (Buysse et al., 1989)	52	2.67	1.70
Heterogeneous Cancer Sample (Beck et al., 2004)	214	8.15	4.70
MDD (Buysse et al., 1989)	34	11.09	4.31
DIMS (Buysse et al., 1989)	45	10.38	4.57

MDD- Major Depressive Disorder

DIMS- Disorder of Initiating and Maintaining Sleep

Table J

Pittsburgh Sleep Quality Index Clinical Cut-off >8

PSQI Global Score	Frequency	Cumulative Frequency	Cumulative Percent
1	2	2	15.38
5	1	3	23.08
6	1	4	30.77
7*	1	5	38.46
9*	1	6	46.15
10	1	7	53.85
11	1	8	61.54
12	1	9	69.23
13	1	10	76.92
14	1	11	84.62
15	1	12	92.31
16	1	13	100.00

Table K

Correlations: QOL Subscale Scores and Global Sleep Quality Scores

QOL Subscale/ Component Score	PSQI Global Score
PF	-0.647 0.017*
RP	-0.700 0.008*
BP	-0.389 0.189
GH	-0.836 0.000*
VT	-0.774 0.001*
SF	-0.494 0.086
RE	-0.259 0.392
MH	-0.411 0.163
PCS	-0.761 0.003*
MCS	-0.361 0.226

Table L
Means by Resection Status

Resection Status	N Obs	Variable	N	Mean	Std Dev	Minimum	Maximum
RO/1	10	PF_NBS	10	48.8	8.9	32.0	57.1
		RP_NBS	10	47.8	12.4	28.0	56.2
		BP_NBS	10	52.9	11.1	37.5	62.8
		GH_NBS	10	49.4	11.8	32.2	64.0
		VT_NBS	10	52.1	11.4	34.9	70.4
		SF_NBS	10	54.4	5.9	40.9	57.1
		RE_NBS	10	52.2	7.1	34.3	55.3
		MH_NBS	10	55.2	8.7	39.1	64.1
		PCS	10	47.9	11.2	27.9	59.2
		MCS	10	55.5	7.0	41.9	64.7
R2a	1	PF_NBS	1	36.2	.	36.2	36.2
		RP_NBS	1	28.0	.	28.0	28.0
		BP_NBS	1	46.5	.	46.5	46.5
		GH_NBS	1	36.8	.	36.8	36.8
		VT_NBS	1	32.5	.	32.5	32.5
		SF_NBS	1	46.3	.	46.3	46.3
		RE_NBS	1	55.3	.	55.3	55.3
		MH_NBS	1	50.4	.	50.4	50.4
		PCS	1	30.4	.	30.4	30.4
		MCS	1	53.9	.	53.9	53.9
R2b	2	PF_NBS	2	32.0	14.8	21.5	42.5
		RP_NBS	2	28.0	0.0	28.0	28.0
		BP_NBS	2	35.3	3.0	33.2	37.5
		GH_NBS	2	28.9	3.3	26.5	31.2
		VT_NBS	2	32.5	0.0	32.5	32.5
		SF_NBS	2	32.7	11.5	24.6	40.9
		RE_NBS	2	29.0	7.4	23.7	34.3
		MH_NBS	2	30.0	6.4	25.5	34.5
		PCS	2	32.8	6.3	28.3	37.2
		MCS	2	31.0	0.4	30.7	31.3

APPENDIX D
ADDITIONAL ANALYSES

	Page
Table M: Estimation of Scores: Physical Component Scores, No Interaction	275
Table N: Estimation of Scores: Mental Component Scores, No Interaction	275

Table M

Estimation of Scores: Physical Component Scores, No Interaction

Parameter	Estimate		Standard Error	t Value	Pr > t
Intercept	40.286	B	4.503	8.95	<.0001
site appendiceal	5.095	B	2.547	2.00	0.049
site other	0.000	B	.	.	.
resect R0/R1	4.071	B	4.149	0.98	0.330
resect R2a	3.567	B	4.371	0.82	0.417
resect R2b	0.000	B	.	.	.

Table N

Estimation of Scores: Mental Component Scores, No Interaction

Parameter	Estimate		Standard Error	t Value	Pr > t
Intercept	56.410	B	3.644	15.48	<.0001
site appendiceal	-0.045	B	2.061	-0.02	0.982
site other	0.000	B	.	.	.
resect R0/R1	-2.814	B	3.358	-0.84	0.404
resect R2a	-3.098	B	3.537	-0.88	0.383
resect R2b	0.000	B	.	.	.